THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1936

ORIGINAL ARTICLES.

PURPURA HEMORRHAGICA WITH LYMPHOCYTOSIS; AN ACUTE TYPE AND AN INTERMITTENT MENSTRUAL TYPE.

By George R. Minot, M.D.,

PROFESSOR OF MEDICINE, HARVARD UNIVERSITY; DIRECTOR THORNDIKE MEMORIAL LABORATORY; VISITING PHYSICIAN, BOSTON CITY HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

The occurrence of thrombopenic purpura associated with a normal or increased number of white blood cells, the majority of which are other than neutrophils, suggests the diagnosis of leukemia. In idiopathic purpura hemorrhagica the neutrophils usually form over 50% of the white blood cells. The absence of leukopenia would practically rule out one or another form of aplastic or aregenerative anemia or "malignant" neutropenia. If anemia is absent, or present only in proportion to the amount of blood lost, it would make the diagnosis of leukemia unlikely, because in this disease, pronounced thrombopenia and hemorrhage seldom occur except relatively late when there is a considerable degree of anemia. If then, upon studying the white blood cells, it is decided that the majority are atypical lymphocytes with none or very few grossly immature cells, one might wonder if the patient had infectious mononucleosis. In that condition, however, purpura with decreased blood platelets is very rare. Tidy[1] located only 5 cases recorded in the literature with purpura, and at least 2 were probably not examples of infectious mononucleosis.

It was this general state of affairs that was presented particularly by the first 3 acute cases I shall describe. The striking feature of the second 3 cases was the occurrence of intermittent purpura hemorrhagica associated with menstruation. In these latter cases there occurred a temporary increase of lymphocytes so that during the period of elevation the cases simulated somewhat the acute cases. All 6 cases terminated favorably.

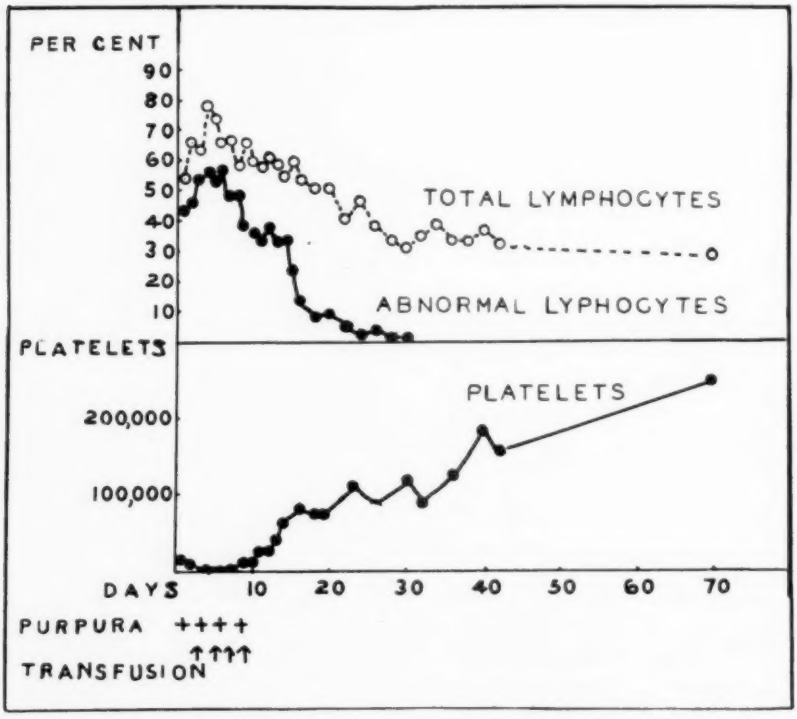


FIG. 1.—Case 1. Acute purpura hemorrhagica with lymphocytosis.

Acute Purpura Hemorrhagica With Lymphocytosis. Fig. 1 records the significant data concerning the lymphocytes and blood platelets in 1 acute case (Case 1) that are also typical for 2 others.

The cells recorded as atypical lymphocytes were similar in the 3 cases. All large lymphocytes, many of which were somewhat atypical, have been included with the atypical lymphocytes. The cells resemble the type seen in infectious mononucleosis. Intermediate sized cells predominated. Irregular shaped cells, lobed and double nuclei, abnormally deeply staining nuclei, abundant cytoplasm with atypical granules, and a considerable variation in the size of cells and nuclei were features. At times many cells

seemed distinctly young and occasionally one suggested a lymphoblast. Very bizarre cells were relatively rare. The cells in Case 2 were probably more atypical than in Cases 1 and 3, but in each instance the cell character was sufficiently peculiar to cause considerable anxiety as to whether leukemia existed or not.

In each case the monocytes were within normal limits. Basophils were absent or very rare. Eosinophils were present, usually 1 to 2% of the white blood cells. There was perhaps a tendency for them to be slightly more frequent when the platelets were low than after bleeding ceased; for example, in Case 1 they were 2.5 to 5% during the former period and not over 2.5% later on. Among the neutrophils young forms were present. The absolute number of neutrophils was never markedly reduced but tended to be slightly below normal when the lymphocytes were at or near the peak of their rise. The white cell counts varied from 6000 to 16,000 per c.mm., being greatest at the height of the lymphocytosis. The red cells showed only the features associated with rapid loss of blood; signs of active regeneration were present. Anemia did not become marked and its degree is noted with the synopsis of salient aspects of each case.

Case Reports. CASE 1.—The patient was a man, aged 21, about 15 pounds underweight for his height, who had had no serious illness. He was subject to "colds" and nasal catarrh; the latter was evident at the onset of bleeding. After feeling tired for a few days in April his gums bled and he noticed purpuric areas on his legs. Purpura rapidly appeared on many parts of his body, and bleeding from the gums and nose became marked. There was slight bleeding from the kidneys and, with the development of abdominal pain, probably hemorrhage into the intestines. Four blood transfusions were given and no hemorrhagic manifestations developed after the twelfth day. At the onset a few lymph nodes were palpable laterally on each side of the neck which, although smaller, remained palpable a week after the bleeding ceased. There was no other enlargement of lymph nodes and the spleen could not be felt. During the period of bleeding, when the platelets were very few and the lymphocytes increased (Fig. 1), the temperature varied from 98° to 100° F. The hemoglobin remained above 12 gm. per 100 cc. The white cell count fluctuated between 6000 and 12,000. As bleeding ceased, the platelets rose and lymphocytes fell. After about a month's convalescence the patient felt and appeared perfectly well, and during the subsequent 2 years showed no signs of hemorrhagic disease.

CASE 2.—Case 2 was entirely similar to Case 1. I am indebted to Dr. J. S. Lawrence for some of the data for this patient, who was a well-developed and nourished man of 23. The chart of his lymphocytes and platelets is almost identical to that for Case 1 (Fig. 1). During the period of bleeding which lasted 10 days, and when the platelets were essentially absent and the lymphocytes elevated, the white cell count varied from 8000 to 15,500, and then for a month remained close to 10,000.

The patient was in robust health until 15 days before purpura was first noticed, in September, when he experienced a mild "head cold" which lasted 4 days. He felt perfectly well during the week before purpura began. There first appeared petechiæ on his legs. Within 24 hours purpura became extreme, extending essentially all over the body, and bleeding from the gums

developed. There rapidly followed very pronounced loss of blood from the kidneys and intestinal tract, so that in the subsequent 10 days he was transfused 9 times, being given *in toto* 4330 cc. of blood. Bleeding then ceased, never to return, as the platelets rose reaching 100,000 per c.mm. in a week. They remained at about this level for a month, and at the end of the next month were about 200,000. Some further increase to normal subsequently occurred. The hemoglobin remained close to normal, chiefly owing to the donors' blood, in view of the marked amount of blood lost. A few slightly enlarged lymph nodes were at first detected in his neck but by the fifth day of bleeding they were considered normal. However, a few moderately enlarged nodes then were palpable in the axillæ, but became normal in size within a week. The spleen was thought to be palpable on the first 2 days of the illness, but was never felt thereafter. The temperature remained usually normal and always within a degree of normal except for three transient rises accountable for by transfusion. This young man has remained perfectly well in the last $3\frac{1}{2}$ years and his blood has shown no abnormality.

CASE 3.—A 10-year-old, well-developed, slightly thin girl; she probably had very mild rheumatic fever at the age of 6 years, when her tonsils were removed. Having felt slightly tired for a month she suddenly developed, in October, an extensive number of purpuric lesions all over her body and severe bleeding from the nose, gums and kidneys. Transfusions of blood were given and no bleeding occurred after the twelfth day. On the third day of her illness when the platelets were virtually absent, the white blood cell count was 16,000 per c.mm., and the lymphocytes 74%, most of which were atypical. On the eighth day the lymphocytes were 64%; the white blood cells 14,000, and the platelets very low. The blood appeared normal 3 weeks after bleeding ceased. The hemoglobin fell to 60% of normal before transfusion and remained over 80% thereafter. During the height of her illness the spleen was transiently palpable at the costal margin and a few lymph nodes were palpable in her axillæ, neck and groins but none were larger than about 2 by 1 cm. The pharynx was slightly injected; thick, sticky mucus adhered to the mucous membrane; there was no discharge from her nose. The temperature remained below 100.3° F. The girl appeared normal during the following year.

In this case the sheep cell agglutinin test was negative. It was not done on the blood of the other 2 patients. In none of these 3 patients was there a history of a recognized allergic manifestation or a history of significant contact with poisons or the taking of any drugs.

SYNOPSIS OF A PREVIOUSLY REPORTED[2] SOMEWHAT SIMILAR CASE. An abnormally thin boy, aged 18, observed in 1921; for 2 months he had felt unusually tired and "out of sorts." Then symptoms of anemia, including shortness of breath and palpitation of the heart, developed over a period of 2 weeks, when a moderate amount of purpura appeared with relatively mild bleeding from the gums and nose and persisted for somewhat over a week. The spleen descended 5 cm. below the costal margin, and lymph nodes were obviously enlarged in the neck, axillæ and groins. There was marked chronic tonsillitis. Fever was only slight. On the fifth day of purpura the hemoglobin was "55 per cent," the platelets about 25,000 per c.mm. and the white cell count 12,000, with 81% lymphocytes nearly all of which were pathologic. Many lymphocytes were more abnormal and immature than in the 3 cases recorded above. The platelets were normal within 2 weeks after the bleeding ceased. The patient slowly improved, the tonsils were removed, and during the following 8 years he remained well.

Discussion. This case, although having much in common with the 3 preceding cases, differs from them in that anemia developed insidiously before purpura appeared, and the lymph nodes and spleen were very distinctly larger. The thrombopenic purpura lasted, however, about the same length of time. The onset with anemia does not suggest infectious mononucleosis, yet the white blood picture and enlarged lymphoid tissue is consistent with that disease, but the marked decrease of platelets is at least very atypical for the condition. Originally leukemia was suspected. In the other 3 cases the onset of illness was abrupt. The part played by the "head cold" which began 15 days before purpura appeared in Case 2 and by a possible upper respiratory tract infection in Cases 1 and 3 is interesting to speculate upon. Did some allergic-like mechanism play a rôle? The outstanding feature of each case was pronounced hemorrhage. The sudden onset of extensive purpura without anemia is at least very rare in acute leukemia or in conditions causing infiltration of the bone marrow with abnormal tissue, and the lymphocytes were not of the type seen in acute leukemia. The course taken at first by the case reported before, with anemia at the onset of illness, simulated leukemia more closely. The lymphoid tissue was less swollen than in the average case of infectious mononucleosis, being very slight in Cases 1 and 2 but distinctly more evident in the 10-year-old girl (Case 3). Fever was an inconspicuous feature, again unlike typical infectious mononucleosis, as is the negative sheep cell agglutinin test in Case 3. Usually in acute idiopathic purpura hemorrhagica the neutrophils are increased, so that the white cell picture of these cases is unlike what one expects in this condition. Shall we call these cases idiopathic purpura hemorrhagica with atypical lymphocyte reactions or atypical cases of infectious mononucleosis with pronounced thrombopenic purpura? Nosography, as Faber has pointed out, is but one means that aids our understanding. The cases illustrate, as do the 3 other cases about to be described, that severe alteration in the blood and serious symptoms can take place and yet recovery occur. I prefer to think of these cases as examples of purpura hemorrhagica with atypical white blood cell response, and this seems to be rather definitely so in the following 3 cases.

Intermittent Menstrual Purpura Hemorrhagica Complicated With Temporary Increase of Lymphocytes. The outstanding feature of the next 3 cases to be described (Cases 4, 5 and 6) was the occurrence of a rapid fall of the platelets to very low levels and the appearance of purpura in association with menstruation, followed by a quick rise of the platelets and cessation of abnormal bleeding, only to have these events recur with the next menses. In the first 2 cases close to the time of one menstrual period the lymphocytes increased and later on fell, and in the third case these cells increased

in association with 2 consecutive menstrual periods. Thus, the blood picture of these cases temporarily resembled that seen in the acute cases.

The usual case of intermittent purpura hemorrhagica, which is rarer than the chronic continuous type, exhibits two or more attacks of hemorrhagic manifestations with periods of thrombopenia at irregular intervals of weeks, months or years. There also occur cases where the platelets remain considerably decreased for years, with bleeding appearing only at varying and less often regular intervals, when there is apt to be a further temporary drop in the platelets. Such cases have also been referred to as intermittent in type. In women with this condition, purpura and bleeding from mucosæ may be prominent only at the time of the menstrual period. Sometimes excessive menstruation is so much more prominent than other bleeding that it appears as essentially the only hemorrhagic manifestation, and splenectomy may be the final procedure to give relief. Rarely in such cases lymphocytes, almost all normal in type, may reach 50%. The relationship of decrease of platelets with abnormal bleeding to menstruation appears to have received little attention. Leschke and Wittkower[3] present briefly most of the scant available information. Some investigators have maintained and others have denied that normally there is some decrease of the platelets close to the onset of menstruation, with a quick rise as the normal blood loss produces a stimulus for more platelets. It is interesting to note that in Werlhof's classic acute case which recovered in about a week the onset was "towards the period of her menses" and this has been true for other such cases. One must distinguish between the occurrence of menorrhagia with the first menstruation occurring in a case of chronic thrombopenic purpura and the onset of purpura hemorrhagica with menstruation. There was nothing to suggest that in Cases 4, 5 and 6 there had been any hemorrhagic disorder before the onset of their periodic purpura hemorrhagica.

Case 4.*—Significant data are presented in Fig. 2. The patient was a divorced woman, aged 40, 5 ft. 1 in. tall, weighing 132 pounds, who had never been pregnant. Her tonsils had been removed, a maxillary sinus opened, and cholecystectomy for stones performed more than 4 years before the present illness began. About 1 month before bleeding commenced, she had recovered from a rather prolonged attack of low-grade pharyngitis which had caused her to feel "below par."

Suddenly, while feeling perfectly well, her gums began to bleed on the day her menstrual period was due in February, 1935. Very soon she felt a stinging sensation in the skin all over her body, especially on her legs. Numerous small petechiæ were found and several ecchymoses about 5 by 7 cm. in size. Within an hour an excessive flow from the vagina began. Her periods had always been normal and regular on a 28-day cycle. She was transfused twice and abnormal bleeding ceased within 3 days. The

* I am indebted to Dr. Alvin G. Foord, of Pasadena, for the data on this case, with his kind permission to report it.

platelets (Fig. 2), which were very few, increased promptly and she soon felt perfectly well and returned to her active work as a trained nurse. Again suddenly while at work, and on the day her period was due, the same symptoms and signs rapidly developed and the menstrual flow was profound. Once more 2 blood transfusions were given and bleeding soon ceased with rapid increase of platelets. She then received 300 Roentgen ray units over her spleen in 14 days when there were essentially no symptoms. As the time for her period approached the platelets fell and she received 2 more blood transfusions. She did not develop purpura and the period which came 5 days late was probably only slightly excessive. She had no fever until the day after the last Roentgen ray treatment (4 days before her period was due). That day fever appeared and persisted for

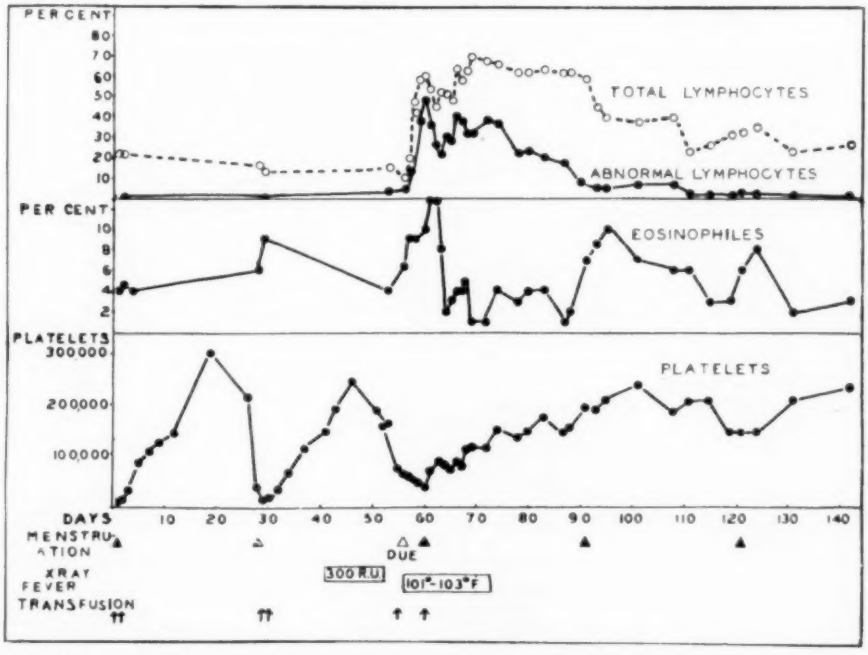


FIG. 2.—Case 4. Intermittent purpura hemorrhagica associated with menstruation. A temporary increase of lymphocytes complicates the picture.

about 20 days; the temperature varied each day from 103°, usually about 102° to 99° or 100° F., being less after about the fourteenth day. With the fever, nausea was very troublesome. Fig. 2 shows the lymphocyte response at this time. The lymphocytes appeared less abnormal than in Cases 1 and 2. At the height of the fever the sheep cell agglutinin test was negative and the same result was obtained about 10 days later. There was no enlargement of the spleen or lymph nodes at any time. The throat and nasal passages were normal. Various types of cultures and agglutination tests and all other examinations were negative, including Roentgen ray examination of the lungs.

At no time was there any noteworthy anemia. Coincident with fever and increase of lymphocytes the white blood cells remained in the vicinity

of 11,000 per c.mm., and before and after this event they were usually about 7000. The eosinophils increased temporarily in association with the menses (Fig. 2). Basophils were very rare. The monocytes were not increased. Young forms of neutrophils were increased after Roentgen ray treatment and remained somewhat elevated during the period of fever.

No evidence of any sort, which was diligently searched for, indicated that the patient had taken drugs or had been exposed to poisons. She gave no history to suggest allergy nor was there a family history of this condition.

Following a convalescent period of about 5 weeks after fever ceased; she has appeared well in the subsequent 9 months.

It seems unlikely that the Roentgen ray treatment was responsible for the attack of fever and increase of lymphocytes, and particularly when the next case to be described which received no such therapy developed the same syndrome. The course taken by the eosinophils will be commented upon after describing the other 2 similar cases.

CASE 5.—This patient, seen 12 years ago, was an unmarried woman, aged 28, whose past history appears to have no bearing on the present illness. She was apparently well when bleeding began but had had a "head cold" about 6 weeks previously. The data for the blood are less complete than in Case 1, but the sequence of events was very similar. She had 2 mild and brief attacks of purpura and menorrhagia at the time of 2 consecutive menstrual periods, followed by much more severe attacks, of only a few days' duration, with the next 2 periods. With the subsequent period there were a few petechiæ on her legs and only slight excess menstrual flow. With each of the latter 3 attacks it is known that the platelets were very few and that they were approximately normal at some time between attacks. As the last attack was subsiding, the lymphocytes rose from about 25 to 63% when the majority were slightly abnormal in type. The white cells were about 14,000 when the lymphocytes remained elevated for about 12 days. During the first 7 of these 12 days the patient had slight fever; the temperature remained about 100.5° F. The white cell count, both before and after the temporary increase of lymphocytes, was about 7000 when the differential white cell count was essentially normal. The eosinophils were 1 to 4%, with perhaps a tendency to be more frequent near the time of menstruation. Anemia was never more than slight, in part prevented by blood transfusions at the time of the severer bleeding episodes.

There was no evidence of respiratory or urinary tract infection, and the lymph nodes and spleen remained normal in size. She gave no history of an allergic condition. It is unknown whether she had taken any drugs.

With the 2 menstrual periods following the rise of lymphocytes there were a very few petechiæ on the legs and the flow from the vagina was slightly excessive. In the next 2 years she had no hemorrhagic manifestations.

CASE 6.—The patient was an unmarried, large-framed woman, aged 26, weighing 160 pounds. The past history was essentially negative except for the fact that she had had, although not for 2 years, a few mild and brief attacks of urticaria due to no recognized cause. There was no history of other conditions suggesting allergy and no history to indicate sensitivity to any known substance.

She had a brief and mild attack of purpura 18 days before the chart (Fig. 3) commences, with somewhat excessive menstrual flow. A blood smear at this time showed the platelets diminished, the lymphocytes 30%, and the eosinophils 5%. Eight days before the next menstrual period she developed a sore throat, and 2 or 3 days before menstruation her pharynx was injected, the tonsils reddened, and fever developed.

The course taken by the lymphocytes and their relationship to the fever is shown in Fig. 3. The abnormal ones were chiefly intermediate in type and relatively slightly abnormal. At no time did the white cell count fall below 6000 or reach above 12,000, the higher counts being recorded when the lymphocytes were elevated. The periodic rhythm of the eosinophils is shown in Fig. 3. The monocytes were 3 to 8%, and the remaining cells were neutrophils. The sheep cell agglutinins were not examined.

The temperature remained elevated for 2 weeks, usually about 100.5° F., rarely 102.5° F., and subsided gradually. During the period of lymphocytosis there were moderately enlarged lymph nodes at the angles of the

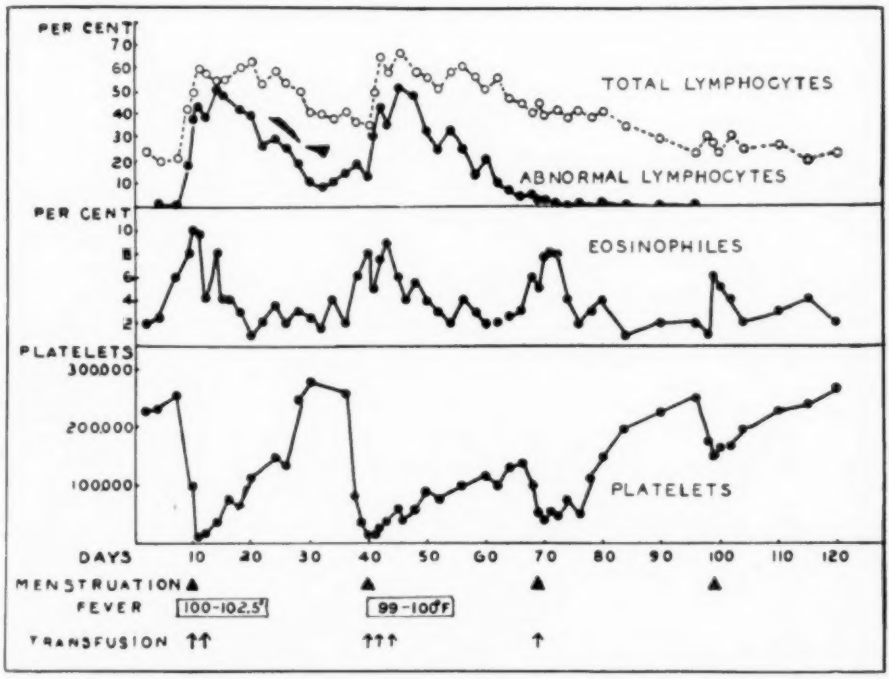


FIG. 3.—Case 6. Intermittent purpura hemorrhagica associated with menstruation. A mild attack of purpura with thrombopenia occurred with menstruation beginning 18 days before the first charted observation.

jaws and in the anterior chains of the neck. No other nodes were abnormally enlarged nor was the spleen palpable. The tonsillitis and pharyngitis remained mild and subsided with the fever; at the same time the lymph nodes receded. After fever had been absent for about 2 weeks and on the day the next menstruation began, the lymphocytes increased once more, the nodes in the neck became more swollen but less so than before, and for the following 15 days the patient had slight fever, the temperature varying from 99° to 100° F. During this time the pharynx and tonsils appeared moderately injected.

With the 2 menstrual periods that occurred when fever was present, ecchymoses and petechiæ appeared especially on the legs, with marked

menorrhagia and slight bleeding from the gums and nose. After blood transfusions, abnormal bleeding ceased within 2 to 4 days. Anemia did not become pronounced. The platelets rose less and more slowly after the second of these two episodes (Fig. 3), but fell equally rapidly just before each of these 2 menstrual periods. At the time of the subsequent period the platelets fell but not to such a low level as formerly; coincident with this only very slight purpura occurred and the menstrual flow was only moderately in excess of normal. Following that period she remained well in the next 2 months, then left this country and has not been heard from.

Discussion. The association of abnormal bleeding and thrombopenia with the menses in these 3 patients suggests some altered endocrine function. If, as some investigators believe, there is normally a drop of the platelets just before menstruation, a great exaggeration of the mechanism causing this might be responsible for the development of purpura. Increased capillary permeability has been shown to occur at the time of menstruation and ovarian dysfunction has been considered a cause of some hemorrhagic conditions. Cases of intermittent purpura hemorrhagica differ distinctly from such cases of hemorrhagic diathesis as described by David,[4] and supposed to be due to altered ovarian function. In those cases the platelets are not reduced. The condition of easy bruising, which is sometimes aggravated at the time of menstruation, especially as the menopause approaches, is also, of course, a separate disorder.

The course taken in Cases 4 and 6 by the eosinophils with their increase at about the time of menstruation and decline thereafter, only to rise again in association with the next period, is rather fascinating to speculate upon. It suggests some endocrine rhythm or allergic mechanism. Eosinophilia occasionally develops from altered endocrine functions and may occur with suppression of anterior pituitary function.[5] The recurrent urticaria that had existed in Case 6 was the only symptom evidenced by any of the 3 patients to suggest an allergic background. Is it possible that the first 2 patients developed some allergic state owing to the upper respiratory infection they had had about a month before purpura appeared? The only infection the third patient is known to have had within months of the time purpura developed was after the first attack of bleeding. Purpura hemorrhagica may be induced in animals by antiplatelet serum and may develop in man as the result of "sensitivity" to certain drugs such as "sedormid" (allyl-isopropyl-acetylurea) and quinin. Various forms of eruptions, not only especially erythema and urticaria, but also ecchymoses and purpura without reduction of platelets occurring periodically with, or in place of, menstruation, have also been thought to be sometimes allergic in nature.[6] Some such cases of vicarious menstruation probably are associated with low blood platelets and, although an allergic mechanism may be operative, the conception of altered endocrine function seems

equally plausible. However this may be, the mechanism causing these conditions remains unknown. The reason for the cessation of the condition in the 3 cases described is as mysterious as the mechanism that initiated the difficulty.

The occurrence of lymphocytosis does not necessarily accompany this type of intermittent purpura hemorrhagica associated with the menses. The lymphocytes were never found to be over about 35% in a case of this sort described to me by the late Dr. Ralph C. Larrabee, where the attacks of purpura recurred for many months, though the ultimate outcome is unknown. I am indebted to Drs. James H. Means and Alfred Kranes for describing to me a case comparable to the 3 described above, in which there was no evidence of increase of lymphocytes or eosinophils. This patient, after many recurrent attacks of purpura associated with menstruation, had none for about a year when they returned.

The cause of the lymphocyte increase in the 3 cases described remains unsolved. The absence of other signs of infectious mononucleosis in Cases 4 and 5 than fever, the blood picture, and the negative sheep cell agglutinin test in Case 4, make it unlikely that both these patients developed this disease in addition to intermittent thrombopenia. In Case 6, which seems unique, the occurrence of throat infection directly before and during the first lymphocyte reaction and apparently present with the second temporary increase of lymphocytes would seem to be in some way responsible for the white blood cell picture. The occurrence of adenopathy with increase of lymphocytes is not rare with infection independent of infectious mononucleosis. The presence of fever with each of the lymphocyte reactions in the 3 patients certainly suggests infection in spite of no local signs of infection in Cases 4 and 5. Even if infection was chiefly responsible for the lymphocytosis, one is led to wonder if altered endocrine function or allergy did not play some rôle in allowing the atypical blood response. In the acute cases with single attacks of bleeding fever was conspicuous by its minor degree or absence, and it occurred only during the time of bleeding. In the intermittent cases fever continued long after bleeding ceased. Another contrast between the lymphocyte responses in these two types of cases is that the abnormal lymphocytes in the acute cases decreased in close association with cessation of hemorrhage, while in the intermittent cases they fell a considerable time after an attack of purpura. It would seem as if more than one cause and mechanism for the lymphocyte responses was operative in the 6 cases, but speculations accomplish no very useful object.

Though significant information is here necessarily limited to simple description, we must always remember that our final aim should be to acquire knowledge of the etiology and pathogenesis of morbid processes, so as to be able to apply proper corrective and preventive measures.

Summary. A description is given of: 1. Three non-fatal cases of acute purpura hemorrhagica (thrombopenic purpura) with pronounced increase of lymphocytes, many of which were abnormal.

2. Three cases of purpura hemorrhagica occurring periodically with menstruation which after from 3 to 7 attacks ceased spontaneously. In association with 1 attack in 2 cases and 2 attacks in the third case a temporary increase of lymphocytes occurred associated with fever.

REFERENCES.

1. Tidy, H. L.: Glandular Fever and Infectious Mononucleosis, Lancet, **2**, 180, 1934.

2. Minot, G. R.: A Non-fatal Case Simulating Acute Leukemia With Anemia and Thrombopenic Purpura, Med. Clin. North America, **13**, 1, 1929.

3. Leschke, E., and Wittkower, E.: Die Werlhofsche Blutfleckenkrankheit (thrombopenische Purpura), Ztschr. f. klin. Med., **102**, 649, 1926.

4. David, W.: Ueber "Purpura"-Erkrankungen bei Frauen, Med. Klin., **22**, 1755, 1926.

5. Rowe, A. W., and Lawrence, C. H.: Studies on Endocrine Glands: II. The Pituitary, Bull. Assn. for Study of Internal Secretions, **12**, 245, 1928.

6. Ellman, P., and Weber, F. Parkes: Recurrent Menstrual Purpura and Vicarious Menstruation, Brit. J. Dermat. and Syph., **47**, 197, 1935.

QUANTITATIVE VARIATIONS IN THE HEMACYTOLOGIC CONSTITUTION OF HEALTHY MEN AND RABBITS.

By Paul D. Rosahn, M.D.,

JOSIAH MACY, JR., FOUNDATION FELLOW IN PATHOLOGY, YALE UNIVERSITY, SCHOOL OF MEDICINE, NEW HAVEN, CONN.,

AND

Albert E. Casey, M.D.,

ASSOCIATE PROFESSOR OF PATHOLOGY, UNIVERSITY OF VIRGINIA, UNIVERSITY, VA.

(From the Laboratories of the Rockfeller Institute for Medical Research, New York City.)

For the past several years this laboratory has been conducting a systematic survey of the genetic constitution of the rabbit, particularly with reference to breed characteristics and hereditary abnormalities. Several methods have been utilized for the quantitative assay of genetic constitution, one of these being the numerical estimation of the various formed elements of the blood. By employing precise technical procedures, and the biometric method of group analysis, numerical constants for each of the blood cells have been defined for the healthy rabbit. Moreover, the reactivity of the animal host, upon receiving the impact of disease, or when subjected to physiologic or environmental stresses, has been studied in terms of the reflected numerical alterations in the blood cytology.

In this and previous reports the term hemacytologic constitution is used to designate the composite blood formula for the individual, race or family. This entity, in conjunction with many others, comprises the summation known as constitution. In a previous com-

munication[1] it was shown that the blood cytology of healthy rabbits of the same breed was more alike than the blood cytology of individuals of different breeds, and that a characteristic and typical blood formula existed for each variety of standard breed of rabbit studied. Since all known variables had been held constant during this investigation, it was concluded that the differences in the blood cytology of different breeds were largely inherited differences. This study it should be noted, was concerned with the hemacytologic constitution of *races* or *breeds* of rabbits. In the present report observations are presented with reference to the hemacytologic constitution of *individuals;* it will be shown that characteristic and typical blood formulæ exist for each of several healthy individuals representing the two species of rabbit and man.

The present report so far as we know offers the only biometric evidence to justify this concept, which, however, has been expressed in more or less similar form by previous investigators. Miller[2] stated that the interpretation of any differential count should be based on a knowledge of that particular person's normal blood picture when possible, on the average values for the locality in which the individual resides, and a consideration of those factors peculiar to the individual which modify that particular blood. Doan and Zerfas,[3] noting that the red and white cells probably change their relative concentrations in the blood from time to time, advocated a zonal concept with adequate individual extremes. Smith and McDowell[4] studied the normal rhythm of the white blood cells in two women subjects, and concluded that the number of white cells varies within certain limits, these limits being different in different persons, and under normal conditions constant in the same person. According to Medlar[5] the greatest value of the leukocytic formula in pathologic states is when the normal leukocytic formula for the individual has previously been established. Shaw[6] concluded that the number of leukocytes is a character of the individual, since the range of variation of the total leukocytes in the year is the same as in one person in 24 hours, but less than in a population. With this conclusion Garrey and Bryan[7] appear to agree.

Material and Methods. The plan of the experiment was as follows: Weekly or biweekly complete blood examinations were made on a group of 6 healthy rabbits and 5 healthy young men. The rabbits were examined over a period of 2 years, the men for 1 year. The mean values for each of the blood cell elements of each individual were then calculated from these repeated observations, and a comparison of the individuals in each group with regard to these mean values was made.

Rabbit Material. When the investigation was begun in the fall of 1930, 10 rabbits comprised the group, but during the ensuing 2 years of observation 4 of them died from intercurrent infection. The available observations on these 4 animals are not included in the analysis. The rabbits were all males of the usual brown-gray hybrid variety, and were approximately 6 to 8 months of age at the beginning of the experiment. Throughout the

observation period they were housed in well-ventilated, well-illuminated rooms. The diet consisted of hay, alfalfa, a commercial food pellet of compressed grains, and a free supply of water.

Human Material. The selection of the young men whose blood cytology is here reported was influenced only by the chance circumstance that they were all active in the same laboratory at the time of the investigation. All had been living in the northeastern part of the country for a minimum period of 5 years, but one or two had made more or less extended trips South and North during this period. The diet was of the usual American type, with slight variations governed by individual predilection. A thorough physical examination was not performed at the beginning or during the observation period; the young men are designated as "healthy" because of their regular attendance in the laboratory and their symptom-free state throughout the study.

Number of Observations. A weekly complete blood examination was conducted on each of the 6 rabbits during the academic year beginning October 30, 1930, and ending June 18, 1931, with 1 examination on June 11 omitted. During the following year biweekly counts were made beginning October 15, 1931, and ending June 23, 1932. Thus during the interval from October 30, 1930, to June 23, 1932, each animal in the group had 51 complete blood examinations,* each made during the period from 9 A.M. to 1 P.M. on the same day of different weeks.

Parallel and similar blood examinations were conducted on the 5 human subjects during the year beginning October 31, 1931, and ending June 23, 1932, with 18 biweekly counts on each individual.

Blood Counting Technique. The pipettes employed were all certified for accuracy by the United States Bureau of Standards. The supravital neutral red technique for differential counting was followed throughout. Platelet counts were made by the method of Casey and Helmer,[8] and hemoglobin estimations with a Newcomber hemoglobinometer. From October, 1930, to June, 1931, each examination consisted of a differential count of 100 cells, a single red cell, white cell and platelet count, and a hemoglobin estimation based on one tube. During the second year, the examinations comprised a differential count of 200 cells, each observer counting 100 cells on different preparations, a red cell and platelet count based on the average finding in the fourth and fifth drops from a single pipette, a white cell count which was the average of the values obtained from the fourth drop from each of 2 pipettes, and a hemoglobin estimation found by averaging the determinations in each of 2 tubes.

During the second year the examinations on both rabbits and men were conducted on the same day of the week and at the same time of the day. The purpose of this procedure was to determine whether the blood cytology of the two species had correlated trends. A preliminary survey has indicated that statistically significant trends for certain blood cells do exist, but this phase of the investigation will not be considered in the present communication. The same two individuals conducted the differential counting examinations, and a single observer made all of the red cell, white cell, and platelet counts and hemoglobin estimations throughout.

Statistical Methods. The successive findings on each of the 5 young men and 6 rabbits were tabulated, and the following statistical constants were determined for each cell factor of each individual: minimum, maximum, mean, standard deviation and stardard error of the mean. The mean is the arithmetic average of all observations on one variate. The standard deviation is the measure of scatter of the individual values about the mean;

* Five platelet counts and 6 hemoglobin estimations on each animal were lost.

99% of the observations will lie between the limits of the mean plus and minus two and one-half times the standard deviation. The standard error of the mean is a measure of the range of scatter of similarly obtained means; 99% of similarly obtained means are expected to fall within the limits described by the mean plus and minus two and one-half times its standard error. In all statistical procedures significance has been attached to values of $P \leq 0.01$; that is, when the probability (P) of an event occurring by chance alone was equal to or less than 1 in 100, the result was considered significant. Similarly, when the probability of an event occurring by random sampling was between 1 and 5 in 100, the result was considered probably significant ($P = 0.01 +$ to 0.05).

In order to determine whether or not significant heterogeneity existed among individuals as regards any single blood element, the method of analysis of variance as modified by Snedecor[9] was employed. The term "variance" is used to denote the square of the standard deviation, that is σ^2. The value "F," calculated for each blood cell element of the two groups, represents the ratio of the larger to the smaller variance. Where the variance between individuals is greater than the variance within individuals, "F" in the text-figures is preceded by a plus sign; in the converse instance, "F" is preceded by a minus sign. In the case of the rabbits, when the value for "+F" exceeds 3.08, significant heterogeneity among individuals has been demonstrated, and probably significant heterogenity when "+F" falls between 2.25 and 3.08. These values represent significance and probable significance when there are 5 degrees of freedom for the greater mean square and 300 degrees of freedom for the lesser mean square. For the men, "+F" must exceed 3.55 to indicate significant heterogeneity, or must lie between 2.48 and 3.55 to indicate probably significant heterogeneity. In this case, these are the values representing significant and probably significant heterogeneity among individuals when the degrees of freedom of the greater mean square is 4 and of the lesser mean square 85. The interested reader is referred to the monograph by Snedecor[9] and the text by Fisher[10] for more detailed information concerning the method of analysis of variance. It should be stated that if heterogeneity among the class means has been demonstrated, then each class is theoretically a sample from a homogeneous population.

The method which has been employed for the graphic presentation of the results has been described in detail elsewhere.[11] The horizontal broken lines in each diagram mark off intervals on the ordinate which are equal to the estimated standard error of the difference between any two means. In all cases this value was obtained by the formula $\sqrt{\frac{2V}{n}}$ * where V represents the "within classes" variance and n the number of observations in any class. This value, although an approximation of the true standard error of the difference between any two means, is sufficiently accurate for graphic purposes. In each instance a test of its accuracy was made by obtaining the average standard error of the several means, and deriving the estimated standard error of the difference between two means by finding the square root of twice the square of this average value.

* Derived as follows:

1. σ mean $= \frac{\sigma}{\sqrt{n}}$. 2. σ difference $= \sqrt{\left(\frac{\sigma}{\sqrt{n}}\right)^2 + \left(\frac{\sigma}{\sqrt{n}}\right)^2} = \sqrt{\frac{2\sigma^2}{n}}$

3. $\sigma^2 = V$. 4. $\therefore \sigma$ difference $= \sqrt{\frac{2V}{n}}$

RESULTS. The results are presented in a series of tables and text-figures. Table 1 gives the following biometrical constants for each of the 14 blood elements of each of the 5 men: maximum, minimum, mean, standard deviation and standard error of the mean. Table 2 summarizes the values obtained by the method of analysis of variance. Tables 3 and 4 present similar data calculated from the observations on the 6 rabbits.

TABLE 1.—THE BLOOD CYTOLOGY OF 5 HEALTHY MEN.

Cell.	Individual.	Maximum.	Minimum.	Mean.	σ	σ mean.
R	A	4720	3780	4293	269	63
	B	5480	4180	4773	402	95
	C	5490	3960	4743	505	119
	D	5560	3980	4653	438	103
	E	5620	4040	4744	430	101
H	A	84.6	55.6	70.9	6.6	1.6
	B	85.9	59.7	72.3	6.6	1.6
	C	81.2	61.2	72.9	5.6	1.3
	D	86.2	62.8	74.5	7.3	1.7
	E	87.3	58.4	74.5	7.6	1.8
P	A	442	264	341	54	13
	B	582	259	371	87	20
	C	435	249	335	49	12
	D	412	243	340	46	11
	E	585	280	391	82	19
W	A	8580	5480	7036	896	214
	B	7730	4980	6383	748	176
	C	8030	4880	6212	784	185
	D	8130	4150	6128	1033	244
	E	8000	4500	5779	921	217
N	A	5472	3299	4551	649	153
	B	4263	2500	3075	483	114
	C	5240	2985	4207	623	147
	D	5647	2387	3802	907	214
	E	5360	2419	3632	712	168
N%	A	71.5	57.5	64.5	3.7	0.9
	B	58.0	35.0	48.9	5.5	1.3
	C	80.5	60.0	67.4	4.9	1.2
	D	69.5	43.5	59.3	7.2	1.7
	E	72.5	53.5	62.5	5.9	1.2
B	A	80	0	31	23	6
	B	132	32	81	31	7
	C	99	0	25	26	6
	D	90	0	46	30	7
	E	96	23	60	24	6
B%	A	1.5	0	0.6	0.52	0.12
	B	1.8	0.5	1.3	0.47	0.11
	C	1.8	0	0.4	0.45	0.11
	D	2.0	0	0.8	0.55	0.13
	E	1.8	0.5	1.0	0.40	0.09
E	A	179	0	91	43	10
	B	946	274	662	164	39
	C	233	0	113	57	13
	D	326	34	184	68	16
	E	676	0	433	159	38

TABLE 1.—THE BLOOD CYTOLOGY OF 5 HEALTHY MEN—(*Continued*).

Cell.	Individual.	Maximum.	Minimum.	Mean.	σ	σ mean.
E%	A	2.3	0	1.4	0.6	0.13
	B	17.3	4.3	10.5	3.1	0.74
	C	4.3	0	1.9	1.0	0.23
	D	4.5	0.5	3.0	0.6	0.15
	E	10.8	0	7.2	2.8	0.65
L	A	2092	905	1490	306	72
	B	2936	1269	1763	412	97
	C	3254	780	1349	524	124
	D	2152	977	1552	338	80
	E	1732	737	1086	259	61
L%	A	25.8	12.3	21.3	4.1	1.0
	B	33.8	21.5	27.4	4.5	1.1
	C	26.0	13.0	20.2	3.3	0.8
	D	36.0	15.8	25.6	4.3	1.3
	E	26.8	13.5	18.9	3.7	0.9
M	A	1383	595	856	199	47
	B	1072	560	781	143	34
	C	1058	102	654	193	46
	D	987	387	681	178	42
	E	860	350	608	162	38
M%	A	18.3	8.5	12.2	2.3	0.6
	B	17.0	8.5	12.3	2.1	0.5
	C	14.5	1.8	10.4	2.6	0.6
	D	16.5	5.8	11.1	2.9	0.7
	E	13.3	6.5	10.6	2.4	0.6

In this and the subsequent tables, the following symbols have been employed: R, red blood cell count in thousands; H, hemoglobin in per cent; P, platelet count in thousands; W, total white cell count; N, absolute neutrophil count; B, absolute basophil count; E, absolute eosinophil count; L, absolute lymphocyte count; M, absolute monocyte count; N%, relative neutrophil count; B%, relative basophil count; E%, relative eosinophil count; L%, relative lymphocyte count; M%, relative monocyte count.

TABLE 2.—THE BLOOD CYTOLOGY OF 5 HEALTHY MEN. ANALYSIS OF VARIANCE.

Cell.	Variance. Between classes.	Variance. Within classes.	σ	σ mean.	σ difference.	F.	P.
R	717580	169260	411.0	97.0	137.0	+4.24	<0.01
H	43.3	46.0	6.8	1.6	2.2	−1.06	>0.05
P	10900	4314	66.0	15.5	21.9	+2.53	<0.05
W	3856370	784320	885.0	209.0	295.0	+4.91	<0.01
N	5555650	475750	690.0	163.0	230.0	+11.68	<0.01
N%	886	41	6.4	1.5	2.1	+21.60	<0.01
B	8914	710	26.6	6.3	8.9	+12.56	<0.01
B%	2.09	0.23	0.48	0.11	0.16	+9.10	<0.01
E	1050113	11970	109.0	26.0	36.0	+87.70	<0.01
E%	268.6	2.9	1.7	0.39	0.56	+94.20	<0.01
L	1110600	142200	377.0	89.0	126.0	+7.81	<0.01
L%	229.6	17.9	4.2	0.99	1.40	+12.81	<0.01
M	205890	31020	176.0	42.0	59.0	+6.64	<0.01
M%	13.9	5.9	2.4	0.6	0.8	+2.36	>0.05

There were four degrees of freedom for the between classes variance, and 85 degrees of freedom for the within classes variance. σ is the square root of the within classes variance. σ mean $= \sqrt{\frac{\sigma}{n}}$, n being the number of observations, 18, in each class. σ difference $= \sqrt{\frac{2V}{n}}$. F is the ratio of the larger to the smaller variance. P represents the degree of significance of F.

TABLE 3.—THE BLOOD CYTOLOGY OF 6 HEALTHY RABBITS.

Cell.	Individual.	Maximum.	Minimum.	Mean.	σ	σ mean.
R	1	6690	4620	5698	484	68
	2	6310	4310	5292	426	60
	3	6200	3970	5119	478	68
	4	6800	3990	5302	737	104
	5	6090	3530	4901	481	68
	6	6190	3890	5004	572	81
H	1	80.5	43.3	63.6	10.1	1.5
	2	76.7	48.7	62.6	7.2	1.1
	3	74.0	44.0	59.3	8.4	1.3
	4	80.7	48.0	62.7	7.0	1.0
	5	69.5	45.0	58.5	7.5	1.1
	6	68.3	44.0	57.0	7.7	1.2
P	1	807	280	503	110	16
	2	887	300	518	121	18
	3	1107	267	520	130	19
	4	687	287	522	119	18
	5	967	304	480	125	19
	6	823	374	556	117	17
W	1	14700	5350	8957	2729	382
	2	12300	5050	7553	1376	193
	3	17850	5800	9665	2289	321
	4	9950	4700	6651	1305	183
	5	10450	5800	7818	1052	147
	6	11800	5450	7881	1340	188
N	1	8379	1712	4223	1160	162
	2	8364	1890	3897	1216	170
	3	10545	1989	4821	1633	229
	4	6156	1718	3174	1056	148
	5	5191	1769	3503	827	115
	6	7906	1600	3559	1166	163
N%	1	68.0	32.0	46.2	7.9	1.1
	2	68.8	27.0	51.1	9.6	1.3
	3	74.0	26.0	50.2	9.6	1.4
	4	72.0	28.0	47.5	8.8	1.2
	5	66.5	25.0	44.8	9.0	1.3
	6	67.0	16.0	45.0	10.8	1.5
B	1	1741	223	808	284	40
	2	1027	98	440	222	31
	3	2534	70	761	399	56
	4	1632	200	612	262	37
	5	1141	148	551	237	33
	6	1388	92	580	261	37
B%	1	20.3	2.0	9.3	3.4	0.5
	2	12.8	1.0	5.8	2.9	0.4
	3	28.0	1.0	8.4	4.7	0.7
	4	17.0	2.5	9.2	3.3	0.5
	5	16.0	1.0	7.1	3.1	0.4
	6	15.0	1.0	7.5	3.3	0.5
E	1	384	0	143	91	13
	2	748	0	152	130	18
	3	1199	0	254	218	31
	4	384	0	139	92	13
	5	523	0	141	122	17
	6	326	0	75	65	9

TABLE 3.—THE BLOOD CYTOLOGY OF 6 HEALTHY RABBITS—(*Continued*).

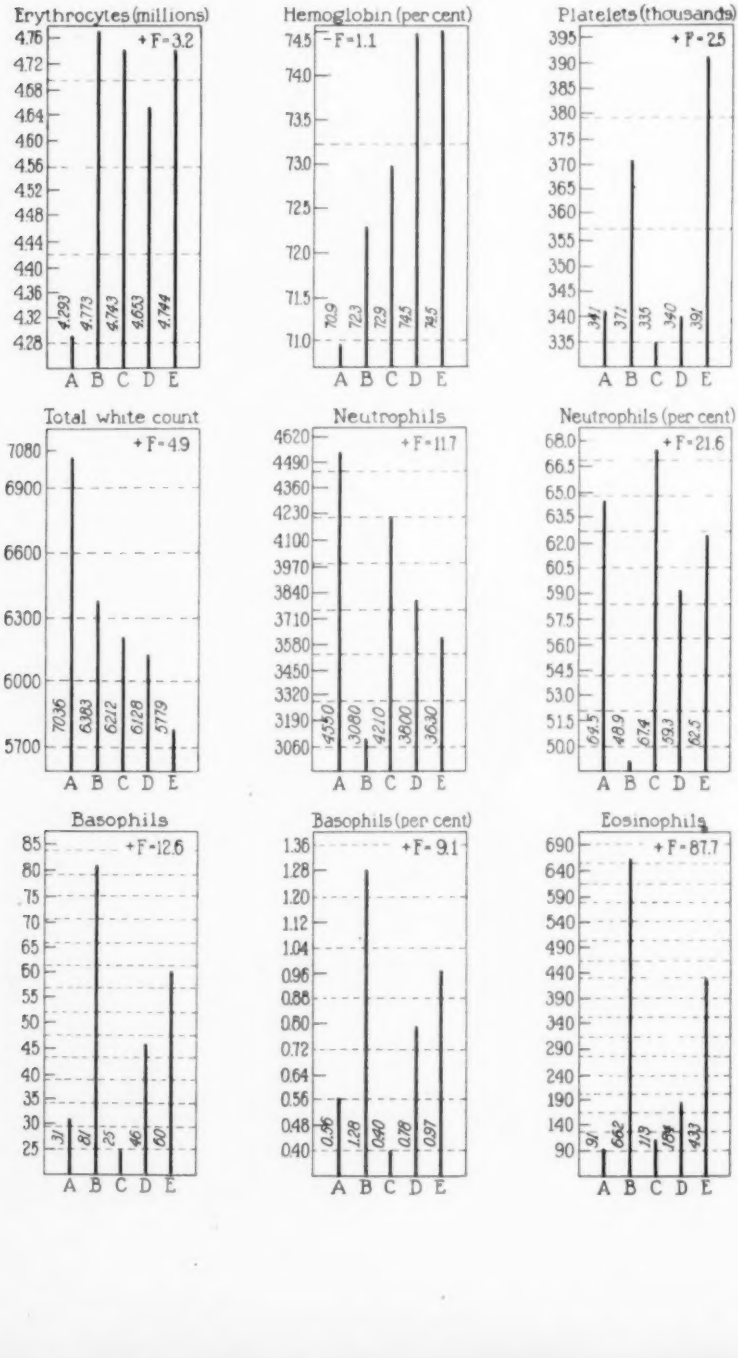
Cell.	Individual.	Maximum.	Minimum.	Mean.	σ	σ mean.
E%	1	4.0	0	1.72	1.10	0.15
	2	8.0	0	2.01	1.43	0.20
	3	11.0	0	2.74	1.89	0.26
	4	5.0	0	2.27	1.37	0.19
	5	8.0	0	1.80	1.57	0.22
	6	4.5	0	1.03	0.88	0.11
L	1	5709	1245	3204	995	139
	2	4472	1320	2524	688	96
	3	7448	1080	3188	1398	196
	4	3791	1089	2186	633	88
	5	6552	1184	3145	879	123
	6	6400	1632	3175	1019	143
L%	1	52.0	15.0	35.2	7.9	1.1
	2	56.0	18.0	33.9	9.1	1.3
	3	56.0	12.0	33.0	10.6	1.5
	4	59.0	14.8	33.0	10.1	1.4
	5	63.0	16.0	40.2	9.2	1.3
	6	65.5	21.0	40.5	11.7	1.6
M	1	1743	145	722	321	45
	2	1353	192	549	231	32
	3	1772	152	609	324	45
	4	1319	0	566	266	37
	5	1392	68	471	253	35
	6	1064	60	493	249	35
M%	1	14.0	3.0	7.7	2.7	0.4
	2	13.0	3.0	7.2	2.2	0.3
	3	14.0	2.0	6.1	2.5	0.4
	4	17.0	0	8.5	3.4	0.5
	5	16.0	1.0	6.0	2.7	0.4
	6	14.0	1.8	6.3	2.6	0.4

TABLE 4.—THE BLOOD CYTOLOGY OF 6 HEALTHY RABBITS. ANALYSIS OF VARIANCE.

Cell.	Variance. Between classes.	Variance. Within classes.	σ	σ mean.	σ difference.	F.	P.
R	3979500	297300	545.0	77.0	109.0	+13.38	<0.01
H	331.5	66.3	8.1	1.2	1.7	+5.00	<0.01
P	28945	13845	118.0	17.5	24.8	+2.09	>0.05
W	58236500	3261700	1806.0	253.0	358.0	+17.85	<0.01
N	17818357	1470083	1213.0	170.0	240.0	+12.12	<0.01
N%	450	88	9.4	1.3	1.9	+5.10	<0.01
B	957738	81890	286.0	40.0	57.0	+11.70	<0.01
B%	96.4	12.8	3.6	0.5	0.7	+7.52	<0.01
E	171300	17057	131.0	18.0	26.0	+10.04	<0.01
E%	16.8	2.0	1.4	0.2	0.3	+8.28	<0.01
L	9818800	957400	978.0	137.0	194.0	+10.26	<0.01
L%	616.7	98.6	9.9	1.4	2.0	+6.25	<0.01
M	417100	77900	279.0	39.0	55.0	+5.35	<0.01
M%	52.3	7.4	2.7	0.4	0.5	+7.05	<0.01

There were five degrees of freedom for the between classes variance, and 300 degrees of freedom for the within classes variance. σ is the square root of the within classes variance. σ mean $= \frac{\sigma}{\sqrt{n}}$, n being the number of observations, 51, in each class. σ difference $= \sqrt{\frac{2V}{n}}$. F is the ratio of the larger to the smaller variance. P represents the degree of significance of F.

The bar diagrams (Text–Fig. 1 and 2) illustrate graphically the significance of the difference between the represented means. The horizontal broken lines block off intervals on the ordinate equal



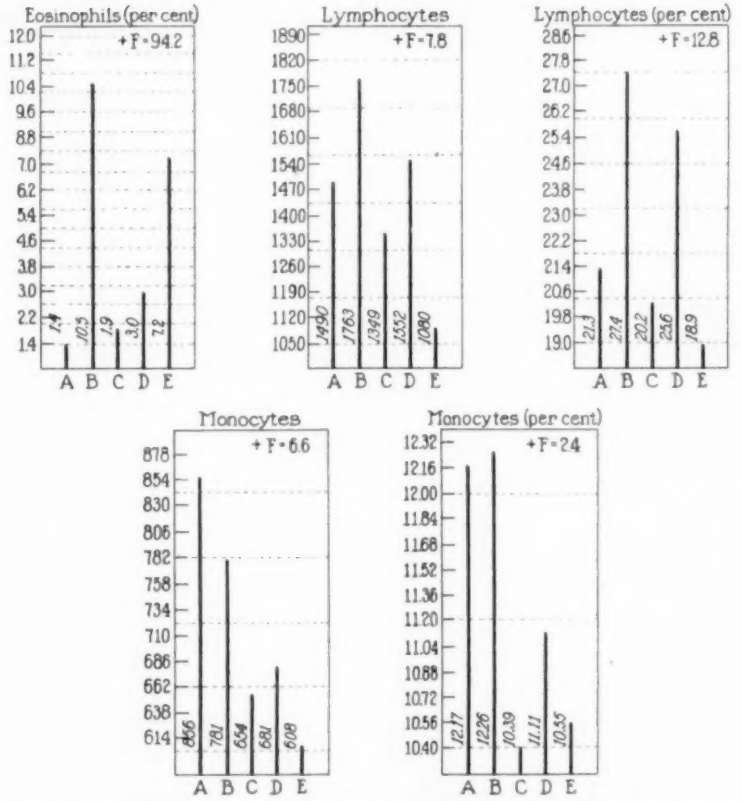
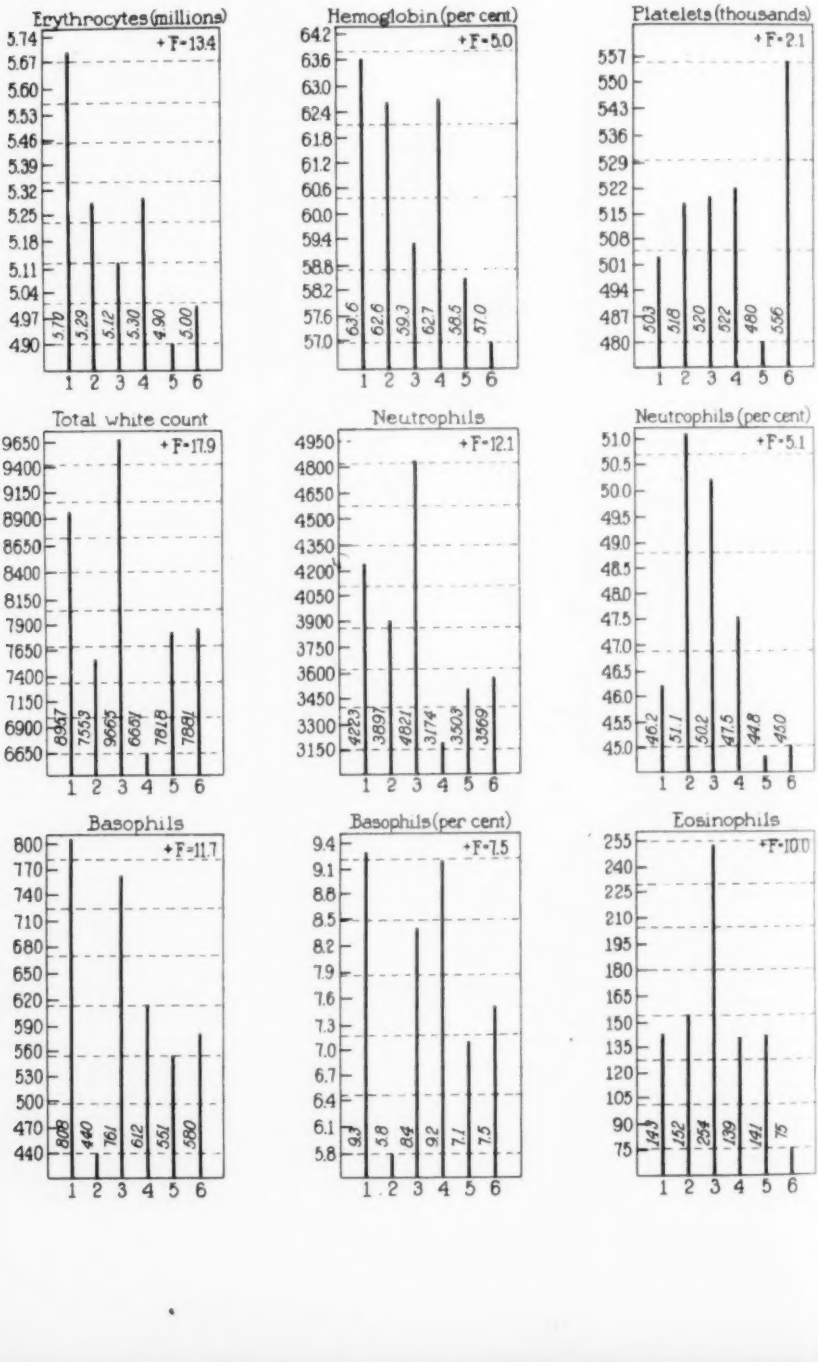


FIG. 1.—Quantitative variations in the blood cytology of healthy men. See text for explanation of horizontal broken lines and significance of "F." A, B, C, D and E represent different individuals.

to the estimated standard error of the difference between any two means. This value was derived as explained above. When the heights of any two vertical bars are separated by at least two and a half intervals, then the populations illustrated are significantly different. For example in the bar diagram headed "Erythrocytes" in Text-Fig. 1, "A" is significantly less than "B," "C," "D," and "E," since it is separated from each of these by more than two and a half intervals. "B" is not significantly different from "C" or "D" or "E", "C" does not differ from "D" or "E" nor does "D" from "E," since in each of these instances less than two and a half intervals separate the mean values depicted. Similarly the significance of the difference between any two values can be ascertained.

The value for "F" is shown in Tables 2 and 4 and at the top of each bar diagram. In all instances, with the single exception of the hemoglobin determinations on the men, "F" is preceded by a plus

sign, indicating that the variance between individuals was in every case but one greater than the variance within individuals. Moreover with reference to the human material, the value for "F" was significant ($P < 0.01$) as regards the following eleven cell factors: red



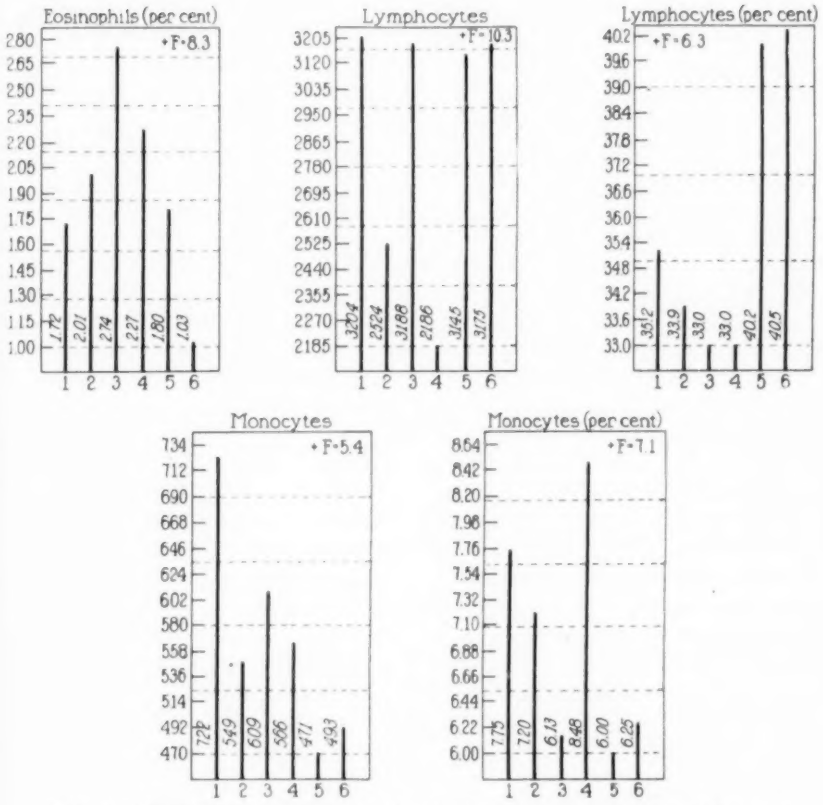


FIG. 2.—Quantitative variations in the blood cytology of healthy rabbits. See text for explanation of horizontal broken lines and significance of "F." 1, 2, 3, 4, 5 and 6 represent different individuals.

cell count; total white cell count; neutrophils, basophils, eosinophils and lymphocytes in absolute and relative numbers; and monocytes in absolute numbers. "F" was probably significant (P = 0.01+ to 0.05) with regard to the platelet count. This indicates that for the factors enumerated significant heterogeneity was found to exist among the individuals studied. Although for monocytes in per cent the variance between individuals was greater than the variance within individuals, tending to demonstrate heterogeneity, the value for "+F" in this instance was not significant. In the case of hemoglobin, the within classes variance was greater than the between classes variance. The difference was however not significant and homogeneity cannot be said to exist.

As far as the rabbit material is concerned, significant heterogeneity among individuals was demonstrated for every factor with the exception of the platelets. In this case the tendency was toward

heterogeneity, but the variance between the means of individuals was not significantly greater than the variance within individuals.

Discussion. The evidence which has been presented indicates that healthy individuals differ widely with respect to their composite blood formula. These differences are all the more striking since they have been shown to occur not only among healthy young men but also among healthy rabbits. In the biometric sense significance is largely a function of the number of observations on a variable, and it is therefore safe to presume that a similar analysis of larger numbers of individuals, with more observations on each than is contained in the present material, would demonstrate highly significant heterogeneity among individuals as regards all of the blood elements studied. This surmise is supported by the fact that with 51 counts on each of 6 rabbits, highly significant heterogeneity was demonstrated for 13 out of 14 blood elements, while the human material, comprising fewer individuals and fewer counts on each, gave evidence of highly significant heterogeneity for only 11 of the 14 factors.

It should be emphasized that the men and rabbits were all in a state of good health throughout the investigation. With 3 exceptions all of the mean values were within the usually accepted limits of normality. The exceptions referred to are the mean red cell count for the young man "A," and the eosinophil counts for the men "B" and "E." Although "A's" mean red cell count of 4.29 $\pm$ 0.06 millions appears to indicate an anemia, this individual has maintained a state of excellent health for 4 years following the reported studies, and moreover repeated counts during this subsequent period have indicated no deviation from this mean value. At no time has his red cell count ever reached five million.

The reason for the high eosinophil count of "B" and "E" is not known with certainty. A plausible explanation would ascribe it to the epidermophyton infection which both of these individuals periodically presented. In this connection however, 3 points should be emphasized: First, that the infections were never severe enough to cause discomfort; second, that high counts were noted during periods when evidence of the affection was absent; and third, that "A" with the lowest eosinophil count was also subject to this disorder. If the explanation for the high eosinophil counts of "B" and "E" is accepted, it is difficult to understand their reactivity to the epidermophyton, and the non-reactivity of "A" to the same stimulus. The suggestion is offered that inherent or constitutional differences among these individuals were largely responsible for their differing reactivity.

Other workers have called attention to what has been termed familial eosinophilia, and it is possible that individuals "B" and "E" fall into this category. Klinkert[12] described a family of 7, 6 of whom had eosinophil counts ranging from 6.2% to 15%. More recently Stewart[13] studied 4 families in each of which several indi-

viduals presented distinct, persistent and unexplained eosinophilia. In none of those so affected could careful investigation reveal any of the known causes of eosinophilia, particularly dermatoses, allergic states or parasitic infections. The eosinophil counts in one of Stewart's families were as follows: father, 2%; mother, 6%; daughters, 10% and 10%; son, 42%. Another remarkable example of familial eosinophilia was the following: mother, 20%; father, 17%; daughters, 32% and 28%; father's brother, 15%; mother's sister, 15%; mother's brothers, 22% and 15%. There was no blood relationship between the father and mother of this family. Poindexter[14] has called attention to the high eosinophil levels among the colored people living in and around Union Springs, Alabama. The average eosinophil count for 158 individuals between 15 and 30 years of age was 8.6%. In none of them was there a positive malarial smear, a positive tuberculin test, parasites in the stool, or any disease generally associated with eosinophilia.

The young men of the present study were all in good heath, in the same decade of life, living in a nearly uniform physical environment, and ingesting approximately the same type of food. The rabbits were supervised more rigorously. Their age, food, and physical environment are known to have been as nearly uniform as laboratory control could make them. The blood counting technique had been standardized by several years of technical improvement, and the studies on the several individuals were carried out by the same observers at the same time of the day, and same day of the week. In spite of this uniformity of environment and of technique, statistically significant differences were demonstrated among the individuals comprising each of the two groups. In the light of our present knowledge, the explanation of these differences is largely a matter of conjecture. It is within the realm of possibility that subclinical infections, or cryptogenic organic disorders might have been responsible for the observed differences among individuals. A more tenable hypothesis however, is suggested by the well-recognized variability of biologic phenomena, particularly of such characteristics as body build, physical comformation, degree of pigment, etc. This hypothesis would ascribe the hemacytologic variations to inherent or constitutional differences among individuals. On this basis the potential blood cell level of an individual is determined by genetic factors, and is as characteristic of that individual as his physical type, the color of his eyes, and even his finger prints. This inherent potentiality is of course subject to the conditioning influence of environmental stresses such as disease, but fundamentally it characterizes and typifies the individual.

The practical implication of this study to the clinician is perhaps of more immediate importance. From the foregoing discussion it is evident that a blood cell count which is normal for one person may in fact be abnormal for another. A total white cell count of 9000 for individual "A" would be within the limits of normal for

him, since it is less than his mean white cell count plus two and one-half times the standard deviation ($7036 + 2\frac{1}{2} \times 896 = 9276$). On the other hand, the same total white cell count of 9000 would represent a pathologic leukocytosis for "E" since this value is greater than "E's" mean count plus two and one-half times the standard deviation ($5779 + 2\frac{1}{2} \times 921 = 8081$). In the same way a red cell count of 3.7 millions for "A" would be within that person's normal range, while the identical count for "B" would be outside his normal limits. If "B" had a neutrophil count of 2000 it would be of little or no clinical importance because this value is inside his normal range ($3075 - 2\frac{1}{2} \times 483 = 1868$) but the same count for "C" would represent a pathologic neutropenia ($4207 - 2\frac{1}{2} \times 623 = 2650$). This study therefore emphasizes the advisability of repeated counts on individuals during health in order to ascertain the numerical variability of each blood-cell constituent. With this knowledge of the blood cells' variability during health as a background, minor fluctuations which would ordinarily be dismissed as of no clinical importance would be assumed to indicate a departure from a healthy status, or in other words, a reaction to a pathologic process.

Summary.—1. Weekly or biweekly complete blood examinations were conducted on a group of 5 healthy young men and 6 healthy rabbits. The rabbits were examined over a period of 2 years, the men for 1 year. The mean values for each of the blood-cell elements of each individual were then calculated from these repeated observations, and a comparison of the individuals in each group with regard to these mean values was made.

2. Statistically significant differences among the men were demonstrated for the following blood factors: red cell count, total white cell count, and neutrophils, basophils, eosinophils and lymphocytes in absolute and relative numbers, and monocytes in absolute numbers. Statistically significant differences among the rabbits were observed for the following: red cell count, hemoglobin in per cent, total white cell count, and neutrophils, basophils, eosinophils, lymphocytes and monocytes in absolute and relative numbers.

3. The evidence indicated that healthy individuals differ widely with respect to their blood formula. These differences were all the more striking since they were shown to occur not only among healthy men, but also among healthy rabbits. It was suggested that the observed differences were due to inherent or constitutional variability among individuals, and that each individual has a characteristic and typical blood formula which is largely determined by genetic factors.

4. The evidence further indicated that a blood-cell formula which is normal for one individual may in fact be abnormal for another. It was therefore suggested that repeated blood-cell counts on individuals during health should be made in order to determine the

numerical variability of the different blood elements. With this information as a background, minor fluctuations which would ordinarily be dismissed as of little or no clinical importance, might be recognized as indicative of an early pathologic process.

REFERENCES.

1. Casey, A. E., Rosahn, P. D., Hu, C. K., and Pearce, L.: Hereditary Variations in the Blood Cytology of Normal Rabbits, Science, **79**, 189, 1934.
2. Miller, S. R.: The Normal Differential Leukocyte Count, Bull. Johns Hopkins Hosp., **25**, 317, 1914.
3. Doan, C. A., and Zerfas, L. G.: The Rhythmic Range of the White Blood Cells in Human Pathological Leukopenic and Leukocytic States, with a Study of 32 Human Bone Marrows, J. Exp. Med., **46**, 511, 1927.
4. Smith, C., and McDowell, A. M.: Normal Rhythm of White Blood Cells in Women, Arch. Int. Med., **43**, 68, 1929.
5. Medlar, E. M.: The Extent of the Variations in the Leukocytes of Normal Individuals, Am. J. Med. Sci., **177**, 72, 1929.
6. Shaw, A. F. B.: A Constitutional Abnormality of the Polymorph Leukocytes with a Record of the Leukocytes for a Period of One Year, J. Path. and Bact., **38**, 259, 1934.
7. Garrey, W. E., and Bryan, W. R.: Variations in White Blood Cell Counts, Physiol. Rev., **15**, 597, 1935.
8. Casey, A. E., and Helmer, O. M.: An Accurate and Practical Method for Blood Platelet Counting, Proc. Soc. Exp. Biol. and Med., **27**, 655, 1930; Casey, A. E.: Further Note on the Enumeration of Blood Platelets and Red Blood Cells, Ibid., **28**, 523, 1931.
9. Snedecor, G. W.: Calculation and Interpretation of Analysis of Variance and Co-variance, Ames, Iowa, Collegiate Press, 1934.
10. Fisher, R. A.: Statistical Methods for Research Workers, 5th ed., London, Oliver and Boyd, 1934.
11. Rosahn, P. D.: A Graphic Method for Representing the Significance of the Difference Between Means, Human Biol., **7**, 267, 1935.
12. Klinkert, D.: Ueber familiäre (erbliche) Eosinophilie, Berlin. klin. Wchnschr., **48**, 938, 1911.
13. Stewart, S. G.: Familial Eosinophilia, Am. J. Med. Sci., **185**, 21, 1933.
14. Poindexter, H. A.: The Differential Blood Picture of a Group of Rural Inhabitants, Ibid., **190**, 416, 1935.

REACTION FOLLOWING INTRA-GROUP BLOOD TRANSFUSION.

IRREGULAR AGGLUTININ DEMONSTRATED BY THE SENSITIVE CENTRIFUGE TEST METHOD.

By C. G. Culbertson, M.D.,
ASSISTANT PROFESSOR OF PATHOLOGY, INDIANA UNIVERSITY, SCHOOL OF MEDICINE, DIRECTOR, CENTRAL LABORATORY,
AND
A. W. Ratcliffe, A.B.,
INDIANAPOLIS, INDIANA.

(From the Central Laboratory, Indiana University Medical Center.)

A NUMBER of cases have been reported in which transfusion of blood between members of the same group has been followed by a typical reaction syndrome of chill, fever, hemoglobinuria, suppression of urine, and azotemia, which may or may not terminate fatally.[1]

While incompatibility of the bloods has been suspected, no etiologic factor has been consistently demonstrated. The prophylaxis remains obscure.

We have recently seen a reaction of this type.

Case Abstract. Mrs. C. was admitted to the maternity ward of the hospital and given a trial labor at the term of a normal pregnancy. Failing to make progress she was delivered by Cesarean section. Considerable blood was lost. Two days later she was given a blood transfusion from her husband who was found to be of the same group (O). Direct cross-matching of the bloods in hanging-drop preparations with 20 minutes incubation at 37° C. showed no evidence of agglutination under the microscope.

At the completion of the transfusion the patient had a chill and her temperature rose to 105° F. This was followed by hemoglobinuria and oliguria for several days, during which time the blood T.N.P.N. gradually rose to 235 mg. per 100 cc. The patient's condition was regarded as critical by the clinicians who saw her. She was given symptomatic treatment, the details of which are outside the scope of this paper. After a very anxious period she gradually recovered; at the end of 7 weeks she was symptom-free and had a normal T.N.P.N. and urine. The patient had never been transfused prior to this time. She gave no history of allergic manifestations.

The compatibility of the bloods was repeatedly checked by the hanging-drop method using the original materials; the original findings were confirmed. This method has been used here and in other hospitals in this city over a period of years without encountering a reaction of this type. The demand for speed in clinical work ordinarily precludes the use of highly sensitive methods. So far as we are able to judge the hanging-drop method is in general use in clinical laboratories.

The compatibility of the bloods was investigated by the centrifuge test method suggested to Wiener and Vaisberg[2] by Landsteiner and Levine. By this method we found that the original sample of recipient's serum agglutinated the cells of the donor. Twenty-four Group O donors were tested by this method; the cells of 23 of these were agglutinated. One (Case 22) was found to be compatible. Neither of the patient's parents were tested. The same individuals were tested by the hanging-drop method. The results of these tests are compared with the results of the centrifuge test method in the table on page 473.

The centrifuge test method was immediately included as a part of the routine procedure.

Samples of the recipient's serum were sent to Dr. Karl Landsteiner who tested it by mixing 1 drop of saline, 1 drop of serum, and 1 drop of 2 to 3% blood suspension in small tubes of 7 mm. diameter. Readings were taken after the mixture had stood at room temperature. Twenty out of 23 Group O bloods with which he tested it were agglutinated. He demonstrated that the agglutinin was not related to either of the factors M or N.

TABLE 1.—COMPARISON OF CENTRIFUGE AND HANGING-DROP METHOD.

Recipient's serum plus cells of donor:	Date: Method: Technician:	11-3-35	11-4-35.	
		Centr. meth. A. W. R.	Hanging-drop.	
			A. W. R	E. S. H.
1		+ + +	0	0
2		+ + +	0	0
3		+ +	0	0
4		+ + +	+ −	0
5		+ + +	0	0
6		+ + +	0	0
7		+ + +	0	0
8		+ + +	0	0
9		+ + +	0	0
10		+ + +	+	0
11		+ + +	+ +	+
12		+ + +	0	0
13		+ + +	+	0
14		+ + +	tr.	0
15		+ + +	+	0
16		+ + +	+ +	0
17		+ + +	0	0
18		+ + +	0	0
19		+ + +	+ +	0
20		+ + +	tr	0
21		+ + +	0	0
22		0	0	0
23		+ + +	+ + +	+ + + (Hemol.)
24		+ +	0	0

In commenting upon the findings Dr. Landsteiner notes that the agglutination in this case is considerably stronger than in most other cases of irregular agglutination reported in the literature.

Our own experience affords no previous cases for comparison. One specimen of Group O blood tested with this serum by the centrifuge method exhibited agglutination as follows:

Serum.	Agglutination.
Undiluted	3 plus
1 to 5 dilution	2 plus
1 to 10 dilution	1 plus

Although its thermal amplitude was not carefully investigated this agglutinin was not noticeably more active at ice-box temperature. Both the laboratory and clinical evidence indicate that it retained some activity at 37° C. This again is contrary to the behavior of most irregular agglutinins that have been reported.

A short time later a similar agglutinin was demonstrated by the centrifuge test method in the serum of a prospective recipient; it had been passed unnoticed in the hanging-drop preparation. This serum agglutinated three Group O bloods tested. The fourth prospective donor (mother of the recipient) was found compatible by both methods. A transfusion of 550 cc. of blood was given with no indication of an unfavorable reaction. Although we attach no significance to the fact, it should be noted that in both cases the intragroup agglutinin was demonstrated during the puerperium.

In our laboratory at the present time the routine procedures in choosing a blood donor include:

I. Grouping the patient (by using sera of Groups A, B, and O).
II. Selection of a prospective donor of the *same* group.
III. Cross-matching (recipient's serum with donor's cells, and donor's serum with recipient's cells) by both:
  (*a*) Hanging-drop, and
  (*b*) Centrifuge-test methods.
IV. Kline test of the donor.

Technique for the Centrifuge Test Method: 1. Place 3 drops of serum in a small test tube (14 mm. diam.).
2. Add 1 drop of cell suspension (3 drops of blood from a 20-gauge needle in 4 cc. of a physiologic saline solution containing 0.2% sodium citrate).
3. Shake to mix. (A control of saline and cells is optional after a little experience.)
4. Incubate 5 minutes at 37° C.
5. Centrifuge 3 minutes at high speed.
6. Note any evidence of hemolysis.
7. Shake the tubes to resuspend the cells while observing them with a concave mirror or hand lens. Note any evidence of clumping.
8. Pour the fluid onto a glass slide and examine microscopically for agglutination.

In our experience this test has not given false positives. Rouleaux formation and pseudoagglutination are less troublesome than in slide methods. In case of question they may be ruled out by repeating the test, using a 1 to 5 dilution of serum. Centrifugalization permits the observation of hemolysis, which rarely may mask agglutination. At the same time agglutination is so sensitized that the research standard of sensitivity is attained without loss of the clinical virtue of speed. While this routine may sound cumbersome, we find that the centrifuge test can easily be set up and completed during the incubation period of the hanging-drop preparations. This additional routine has not slowed up the laboratory service. While it is probable that the hanging-drop method eventually may be discarded, we are not yet ready to do this.

Summary and Conclusions. The relation of anomalous agglutinins to transfusion has been an unsettled question.[3–6] It might be questioned that the agglutinin was responsible for the reaction in this case. However, the facts may be summarized as follows: a Group O patient was given 500 cc. of Group O blood; the cells of this blood were susceptible to agglutination by an anomalous agglutinin of low titer existing in the serum of the recipient. The recipient exhibited the typical symptoms of a delayed transfusion reaction, followed a typical course, and eventually recovered. A second patient, exhibiting a similar anomalous agglutinin, was given 550 cc. of blood compatible with her intragroup agglutinin and no sign of reaction was observed. Until the contrary is shown we shall continue to regard incompatibility resulting from anomalous agglutinins as a definite contraindication to transfusion with such a blood.

In each of the 2 cases the low-titer intragroup agglutinin was unobserved in the routine compatibility tests by the hanging-drop method although it was readily demonstrated by the centrifuge test method.

It is suggested that the use of the centrifuge test method in clinical practice may aid in avoiding transfusion reactions of the type mentioned above.

REFERENCES.

1. McCandless, H. G.: A Hemolytic Blood Transfusion Reaction with Oliguria, J. Am. Med. Assn., **105**, 952, 1935.
2. Wiener, A. S., and Vaisberg, M.: Heredity of Agglutinogens M and N of Landsteiner and Levine, J. Immunol., **20**, 371, 1931.
3. Ottenberg, R., and Johnson, A.: A Hitherto Undescribed Anomaly in Blood Groups, Ibid. **12**, 35, 1926.
4. Landsteiner, K., and Levine, P.: On Isoagglutinin Reactions of Human Blood other than Those Defining the Blood Groups, Ibid., **17**, 1, 1929.
5. Lattes, L.: Individuality of the Blood, Oxford University Press, London, 1932.
6. Wiener, A. S.: Blood Groups and Blood Transfusion, Charles C Thomas, Springfield, Ill., 1935.

SPLENECTOMY IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS.*

By David Riesman, M.D.,
PROFESSOR OF CLINICAL MEDICINE, GRADUATE SCHOOL, UNIVERSITY OF PENNSYLVANIA,

John A. Kolmer, M.D.,
PROFESSOR OF IMMUNOLOGY, TEMPLE UNIVERSITY, PHILADELPHIA, PA.,

AND

David Polowe, M.D.,
PATERSON, N. J.

In subacute bacterial endocarditis as in Hodgkin's disease we know we are beaten from the start. Remissions may occur, raising the elusive hope of recovery but the end is early death. There are a few exceptions to this in subacute bacterial endocarditis but they are so few as to be negligible. We feel somehow that the patient infected with the mildly pathogenic Streptococcus viridans ought not to die. If the streptococcus is only a secondary invader as several authors maintain, then it behooves us to find the primary factors that enable it to become so irresistible an enemy. The interesting point made by recent writers that subacute bacterial endocarditis is only another manifestation of rheumatic infection needs further investigation. Our own impression is to the contrary.

Every imaginable agent and procedure has been used and practically all have been failures. This tragic fact led one of us a few years ago to the following reflections. Is it possible that death is due chiefly to the manufacture of bacteria and toxins in secondary

* Read at the Meeting of The Association of American Physicians, Atlantic City, May 5, 1936.

foci and if so, is the spleen not likely to be the most important branch factory? In the majority of cases the spleen is greatly enlarged and the seat of multiple infarctions. Furthermore, in what is perhaps an analogous situation, syphilitic splenomegaly, it has been found that treatment is sometimes unavailing until after splenectomy.

On the basis of these considerations one of us,[1] in 1918, proposed splenectomy as a therapeutic procedure in subacute bacterial endocarditis and reported a case which is briefly summarized here, as Case 1.

Case Abstracts. CASE 1.—The first case was that of a man, aged 57, father of a medical colleague. On account of a large spleen and anemia with leukopenia the diagnosis of splenic anemia had been made. However, the finding of petechiæ, the presence of a valvular murmur and the long-continued fever justified the diagnosis of subacute bacterial endocarditis, although the spleen was larger than is usually seen in such cases. As nothing had helped the patient, he and the doctors concerned readily accepted the suggestion of splenectomy. The organ was found to be the seat of numerous infarctions. So striking was the improvement that it encouraged the hope of cure. However, 4 weeks later the patient developed an abscess of the larynx from which he died.

CASE 2.—The second case is that of a married woman, aged 25, who had two attacks of rheumatic fever, one at 11, one at 14. At the age of 20 she had auricular fibrillation lasting 2 weeks. Her marriage was followed by two pregnancies that had to be terminated artificially because of the condition of her heart. On June 20, 1935, she consulted one of us because of a tired feeling and painful subcutaneous nodes on fingers and toes. Physical examination showed marked cardiac enlargement, a mitral systolic murmur and 2 painful ecchymotic nodes. Her general appearance was, however, that of a woman in good health. Blood culture yielded a Gram-positive nonhemolytic streptococcus. The patient complained bitterly for a few weeks of pain in the right hip joint and in the abdomen. The blood counts are given in Table 1. Throughout the patient's illness the urine aside from a trace of albumin was entirely normal.

In addition to general supportive measures several specific forms of treatment were instituted—blood transfusions and specific bacteriophage therapy—the phage was kindly prepared by Dr. J. W. P. Love. It proved unavailing and this was also true of snake venom therapy. A total of 10 cc. of a 1 to 3000 solution of moccasin snake venom was administered. There was a transient lessening of the severe hip-joint pain, but after a few injections the pain returned and was worse than ever. The slightest jarring of the bed would make the patient cry out with pain.

It was decided to remove the spleen which had been palpable since early in July, 1935. At the operation the organ was found large and infarcted. Two pea-sized accessory spleens were also removed. There was immediate relief of joint and abdominal pains, an improvement in the red cell count and hemoglobin percentage, no further loss of weight, the heart became quiet and as the patient often stated "it had ceased to tumble about so." The fever continued and seemed to exhilarate her. She saw her friends, played bridge in bed and did not seem to realize that she was critically ill. There was no let-up however in the showers of emboli in the fingers and toes. On December 16, the patient began to develop thickness of speech and nocturnal Cheyne-Stokes breathing which were interpreted as of cerebral embolic origin. On January 1, 1936, she was seized with convulsions and died on the following day.

FIG. 1.—Case 2. Enlarged spleen showing wide vascular band of adhesion.

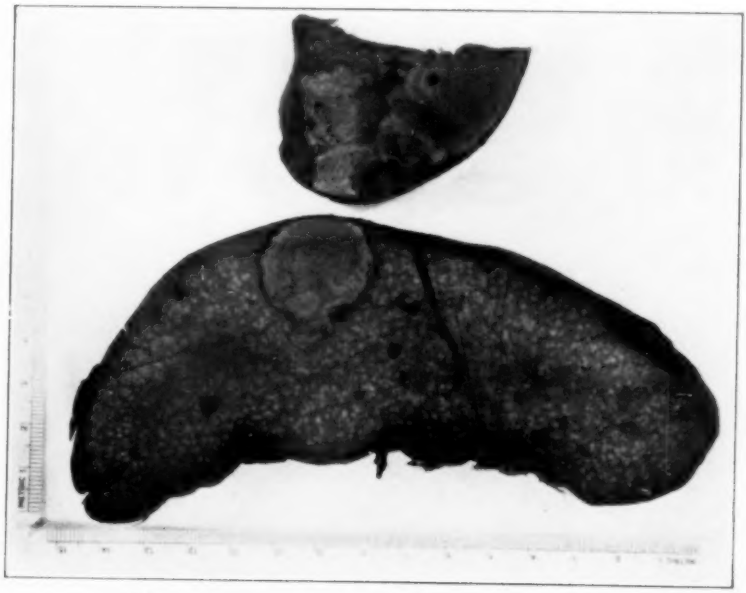


FIG. 2.—Case 3. Section of spleen showing infarcts.

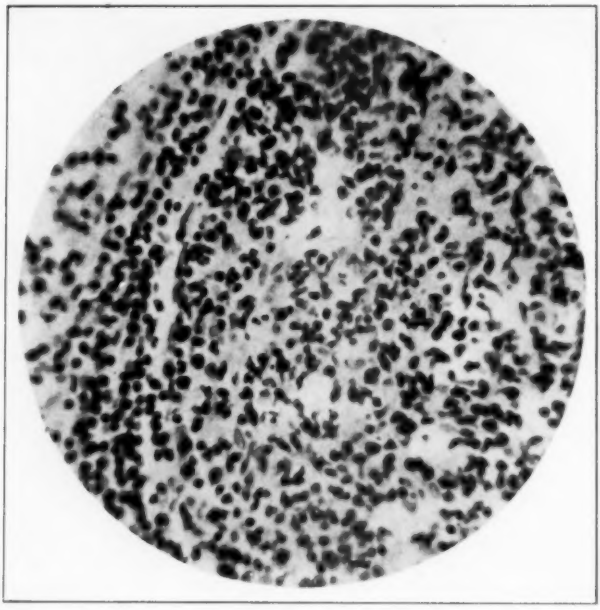


FIG. 3.—Case 2. Part of a lymph follicle near the periphery. Within the follicle are seen histiocytes and neutrophils. In the perifollicular area are found neutrophils and eosinophils among other cells. (× 243.)

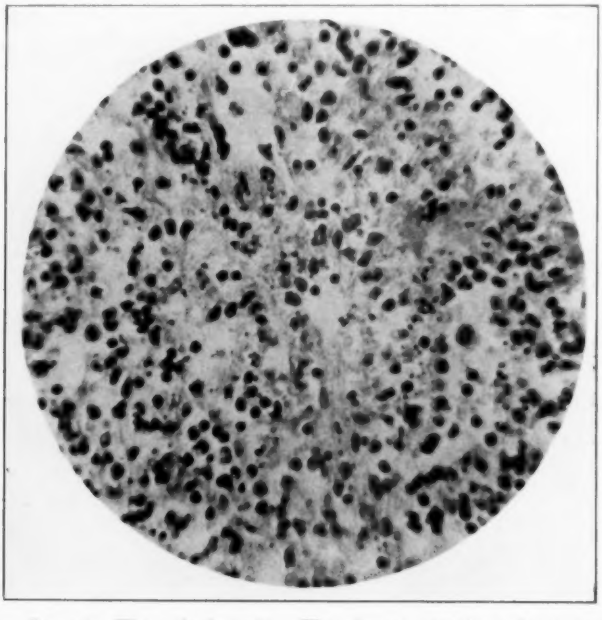


FIG. 4.—Case 2. The splenic pulp. The sinuses contain a large number of neutrophils, lymphocytes and histiocytes. In the pulp proper, there is an accumulation of plasma cells around the bloodvessels. A moderate amount of fibroblastic proliferation is present. The iron pigment is not very abundant. (× 243.)

Examination of the Spleen. Gross Morbid Anatomy. The main spleen was at least twice normal size, of firm consistency, deep red in color and covered by a fine frost of fibrinous exudate. A strong, wide, vascular band of adhesion connected the visceral surface and anterior tip of the spleen to the cardiac portion of the greater curvature of the stomach (Fig. 1). After 10 days in formalin, the spleen weighed 13 ounces (404.3 gm.). A cross-section exhibited large lymphoid aggregations over the entire cut surface, except where the infarct presented itself.

Histologic Examination (Dr. Paul Klemperer). Follicles: These are really large, with centers particularly conspicuous. There is a great number of reticulum cells. But there are also neutrophils within the center of the follicles. Around the follicles, in the perifollicular zone, there is a great accumulation of leukocytes and eosinophils among other cells.

Red Pulp. The sinuses and sinus epithelium are not particularly conspicuous. The sinuses contain a large number of neutrophils, lymphocytes and histiocytes. In the pulp proper there is an accumulation of plasma cells around the bloodvessels. Moderate fibroblastic proliferation is present. There is a good number of pale nucleated cells (histiocytic cells) which contain iron pigment. The iron pigment is not very abundant (Figs. 2 and 3). Gram-stained sections: no bacteria found.

TABLE 1.—THE BLOOD PICTURE IN CASE 2.

Date.	R.B.C., millions.	Hb., %.	W.B.C.	Neutrophils, %.	Band forms, %.	Eosinophils.	Basophils.	Other lymph.
			*Pre-operative.**					
6/22/35	3.9	74	9,900	63	8	0	1	36
7/ 9/35	3.8	79	10,300	75	†	0	2	23
7/24/35	†	76	10,800	75	†	2	1	22
7/30/35	†	83	7,400	70	12	0	2	28
8/ 3/35	4.4	84	6,800	75	15	1	0	24
8/ 7/35	†	†	8,000	61	8	1	1	37
9/14/35	3.7	65	12,800	78	†	2	0	20
			Postoperative.					
9/19/35	4.1	66	14,300	77	15	5	0	18
9/24/35	3.8	74	21,600	79	10	5	0	16
10/ 1/35	3.5	70	14,700	72	14	2	0	26
10/ 8/35	4.1	73	21,100	75	14	2	1	22
10/23/35	4.1	75	14,700	70	9	1	0	29
11/20/35	4.0	73	26,600	77	20	1	0	22
12/16/35	4.4‡	67	29,900	73	12	0	1	26

* The platelet count before splenectomy was average normal (no actual count was made, but that is the note that appears on the blood count sheet as of July 24, 1935). Following splenectomy platelet counts were made on September 19 and 24 and October 1 and 8; these were found, respectively, to be 356,700, 253,440, 310,000 and 258,000.

‡ The blood count should be evaluated in the light of the presence of edema—the patient had gained 5 pounds of fluid in 2 weeks, although there was only slight pitting on pressure of the dorsum of the foot; a slight clubbing of the fingers, from which the blood for counting was taken, was also present, but this was present from the beginning. (Clubbing of fingers first noted, September 29, 1935.)

† Not done.

CASE 3.—I. A., a youth aged 22, was seen in consultation with Dr. Blumberg by two of us on separate occasions. The patient presented the typical picture of subacute bacterial endocarditis. His illness had begun on March 25, 1935, with malaise, muscular pains and late afternoon fever. The symptoms and the laboratory data were characteristic of the disease. Blood cultures—many were made—were positive for Streptococcus viridans.

Despite every form of treatment the disease progressed rapidly downward.* A cerebral embolus produced hemiplegia and stupor. His condition was such that it was felt the end was near. The parents consenting to the operation, it was performed on September 15, 1935, by Dr. W. W. Babcock. The spleen was found enlarged and showed infarction.

Notwithstanding the patient's critical condition the operation was well borne and was followed by striking amelioration. Weight and appetite markedly improved; there was less pain and greater comfort, less sweating, slight reduction of the leukocytosis and greatly improved morale. Unfortunately this favorable course persisted for only 10 days, then the former picture returned. Death took place on December 22, a little over 2 months after the operation.

Examination of the Spleen (Dr. H. J. Lemon). *Gross Description.* The spleen measures 17 by 10.5 by 4.5 cm. It is reddish-brown. The capsule is smooth and the organ is fairly soft. Scattered over the surface are several slightly raised areas which are yellowish-brown, the largest about 1.5 cm. in diameter and 2 cm. in depth, which appear to be abscesses. There is also a small accessory spleen, 1.2 cm. in diameter (Fig. 4).

Microscopic Description. Numerous sections of the spleen show many Malpighian corpuscles, much larger than are normally seen. The enlargement is predominantly of the so-called germinal centers. These are surrounded by a broad zone of lymphoid cells. There are patchy areas of congestion present. Here the sinuses are filled with red blood cells and lymphocytes. In other areas the sinuses are partly empty but appear enlarged. The splenic cords appear thickened and contain many lymphocytes and neutrophils. Large areas of necrosis are present in which there are numerous collections of neutrophils. Active fibrosis is beginning around the edges of the infarcted areas.

Diagnosis. Subacute splenitis with infarcts.

CASE 4.—H. M., aged 39, had no history of rheumatic infection. His illness began in January, 1935, with lack of "pep," weakness, irritability, and so on. In February he had an attack of grippe from which he never fully recovered. On biliary drainage (Dr. H. S. Davidson), the culture yielded a nonhemolytic streptococcus. In May, the man felt somewhat better and continued at work but began to have late afternoon fever. Blood cultures were negative. Somewhat later a thorough study of the patient's case was made in Youngstown, Ohio—Hodgkin's disease and leukemia were suspected.

When seen in Atlantic City he had the typical symptoms of sepsis—chills, fever and drenching sweats. The heart sounds were exceedingly feeble, indeed scarcely audible, but there was no murmur and no arrhythmia. The liver was enlarged and slightly tender. The spleen was easily palpable.

TABLE 2.—SOME BLOOD COUNTS FROM CASE 4.

	8/10/35.	9/26/35.	11/4/35.	4/29/36.	5/11/36.
R.B.C.	4,600,000	3,790,000	4,550,000	4,500,000	4,401,000
W.B.C.	5,750	1,850	9,350	17,400	13,600
Hemoglobin	11 gm. (66%)	9 gm. (54%)	11.5 gm. (69%)	12.5 gm. (73.7%)	12 gm. (70.8%)
Eosinophils	0	4	2	1	1
Mononuclears	19	14	16	9	12
Neutrophils	67	44	70	73	78
Lymphocytes	13	38	10	16	8
Basophils	1	0	2	1	1
Color index	0.71	0.71	0.76	0.81	0.8

* The following were the more specific measures employed in this case: Intravenous and intramuscular injections of Streptococcus cardioarthriditis serum (Small) and concentrated polyvalent antistreptococcus serum, intravenous injections of bacteriophage prepared by Dr. John Love and one of us, transfusions of blood for a total of 19; intravenous injections of sodium cacodylate, and so on.

As the disease progressed the patient lost more and more weight, a total of about 60 pounds. His color became sallow, he grew weak and very irritable and had an extreme hyperesthesia of the skin of the entire body. The spleen was much enlarged and a little fluid could be detected in the abdomen.

No definite diagnosis was arrived at—mural subacute bacterial endocarditis seemed reasonable. As nearly every conceivable treatment had been tried without any result, splenectomy was suggested as a last resort. The patient readily acquiesced and the operation was performed by Dr. Babcock on October 1, 1935.

It was exceedingly well borne, and for about 8 or 9 days the patient appeared distinctly improved. However, on October 11 the temperature began to run in the same manner as it had prior to the operation, but on October 23 it suddenly dropped to subnormal. The patient had a convulsive seizure and was comatose, almost pulseless, and death was expected at any moment. Under stimulation he revived and from that time on his improvement was rapid and progressive. On November 4 he was discharged convalescent. He returned to work and when last seen was in very good condition.

Bacteriologic examination of the spleen revealed a pure culture of Streptococcus viridans.

It is difficult to explain the cause of the collapse of H. M. 23 days after the splenectomy, but following it there was no doubt of his rapid return to normal and a state of satisfactory health. During recent weeks he has had 3 periods of fever with pain in the left loin, sweats and leukocytosis. It is possible that he is developing a perinephric abscess, although the studies with that thought in mind have been negative. Whether the morbid process underlying these attacks is the same as that which afflicted him originally or whether what is going on now is something left over from the operation cannot at present be decided. Dr. Harold Davidson, the family doctor, is convinced that the patient was dying when we saw him together and that the splenectomy saved his life. He gained 60 pounds in weight and for 5 months has been to all intents and purposes a well man.

Examination of the Spleen (Dr. Frank Konzelmann). *Gross Description.* The specimen measures 18 by 12 by 6 cm. The surface is bluish-red and nodular. There is some wrinkling of the capsule. The pulp is moderately firm. The incised surface is a deep red; it is granular. The follicles are few and barely visible. The trabeculæ are not marked. There are occasional translucent irregular whitish markings throughout the organ. There is no evidence of thrombosis of the splenic vein.

Microscopic Description. (Bouin fixation, hematoxylin and eosin.) The follicles are few in number; the number of lymphocytes composing them is also small with a decidedly eccentric arrangement of cells that are somewhat larger than ordinary lymphocytes and cells that have a somewhat more reticular nucleus. The periphery of these small follicles is frequently the seat of hemorrhage. In the interfollicular areas the usual splenic sinuses are almost obliterated by what seems to be swelling of the reticulum. The number of free cells and of lymphocytes seems to be distinctly diminished, while the number of reticulum cells, notably cells that have oval or elongated nuclei, seems to be increased. Occasionally a large cell measuring 30 to 40 microns in diameter with an equally large nucleus is seen. The nucleus of this cell consists of a deep-staining membrane, huge nucleoli and a very scant scattering of chromatin particles. Occasionally there are patches in which several giant cells occur, possessing 2, 3 or 4 nuclei of the type just described. These cells make one think of the Reed-Sternberg cell of Hodgkin's disease. However, the absence of the other cellular elements of Hodgkin's disease makes such a diagnosis improbable. Occasionally mitotic figures are seen among the reticulum cells. The striking feature is the relatively small amount of blood in the organ. There are

patches, especially around the follicles, as mentioned above, where vessels are engorged. An occasional engorged venule is seen, and very careful search reveals here and there pools of blood in very much distended sinuses. It seems as if these bloody collections are most numerous where nodules appear on the surface of the organ. It is also noteworthy that many of the arterioles are characterized by a hyalin degenerative process of the endothelial lining and sometimes of the tunica media. Examination with oil immersion reveals in some of the macrophages small granules that are suggestive of coccoid bodies. Nothing resembling Leishman-Donovan bodies can be discovered.

Diagnosis. Chronic splenitis showing hyperplasia of the fibrous and cellular reticulum.*

The literature on splenectomy in septic conditions, particularly in subacute bacterial endocarditis, is exceedingly meager. The senior author's case was apparently the first to be reported. Of 2 patients with subacute bacterial endocarditis operated in the Mayo Clinic, 1 lived 3 months, 1, 7 months after the operation. We found one article in the Russian literature by Sawadski[2] in which a successful splenectomy is reported. The case was not altogether typical of endocarditis but it was one of long-continued fever in a woman of 28 with a rheumatic history. Sawadski believes that the spleen may act as a focus of infection and says, specifically, that the presence of bacteria in the blood stream is no contraindication to the operation of splenectomy.

Persistent search has revealed a few additional articles. Wieden[3] reports a series of cases of splenectomy from Prague. Among 81 instances of splenectomy, there were 5 cases of endocarditis in which the operation was done for infarcts of the spleen. The first case was that of a military officer of 21 who had had a long-standing sepsis following a grenade injury. After removal of the spleen, which was enlarged and contained several infarcts, the patient recovered completely. While the clinical diagnosis was endocarditis, the possibility of chronic sepsis secondary to wound infection cannot be excluded. The second patient, a man of 40, with a history of rheumatic fever, cardiac enlargement and a systolic and diastolic murmur, was evidently a case of subacute bacterial endocarditis. He died without any improvement in his condition 2 months after the operation. The third case, that of a young woman of 24, with the symptoms of subacute bacterial endocarditis, died 3 months after the operation. The fourth patient was a woman of 57 with symptoms of sepsis, a systolic murmur at the mitral area and enlargement of the spleen. On removal the spleen was found enlarged, with numerous infarcts and hemorrhages. The patient

* Since writing the foregoing article the patient, H. M., was operated upon in the suspicion that he might have a perirenal abscess. No abscess was found. He died in his home in Atlantic City on June 10. No autopsy was obtained. Dr. Kolmer, one of the attending physicians, thinks that death was due to subacute bacterial endocarditis. Whatever the nature of the process may have been, the fact remains that when splenectomy was done the patient to all intents and purposes was near death. He lived nearly 7 months and for most of that time was in good health and able to look after his business.

recovered, but 7 months later there was a recurrence followed again by improvement. A year after the operation signs and symptoms of lymphatic leukemia appeared and the patient died in coma. The autopsy showed lymphatic leukemia and mitral and aortic endocarditis. The fifth patient was a man of 27 with a history of rheumatic fever. He had a murmur and a large spleen. The spleen on removal was found to be the seat of infarcts the size of walnuts. On culture nonhemolytic streptococcus and staphylococcus were obtained. Death occurred 20 days after operation from cerebral embolism.

Vogel,[4] in a lengthy article on extirpation of the spleen in diseases of the blood, says that he wants particularly to recommend splenectomy in the early stages of endocarditis lenta when the general state of the body is adequate and the heart lesion has not progressed too far. He does not think that the continued reinfection of the blood stream is derived from the vegetations on the valves which in the beginning are certainly very slight, but believes it not impossible that a chronic focus of infection such as might be in the spleen overflows into the blood. It is also possible that the bone marrow is a source of sepsis.

Nordmann[5] performed splenectomy in a case of endocarditis in the belief that the spleen might be responsible for the continuance of the infection, by being a reservoir for bacteria and toxic substances. His patient had mitral stenosis and insufficiency as the result of an acute attack of rheumatic fever. Two years later the symptoms of subacute bacterial endocarditis manifested themselves. After 6 months of septic fever uninfluenced by treatment, Nordmann extirpated the infarcted spleen. The patient made a complete recovery and "long ago left the clinic a well man."

Münzer[6] recommended splenectomy but reported no cases in which the operation had been performed.

We have found 1 case in the Spanish literature reported by Escudero and Merlo,[7] of Buenos Aires. The patient at the age of 24 had had an attack of polyarthritis; later a syphilitic chancre for which he was actively treated. When 28 years old the signs and symptoms of subacute bacterial endocarditis appeared—there was mitral insufficiency, hypochromic anemia and severe pain in the left hypochondrium. Blood culture yielded Streptococcus viridans. Splenectomy was performed and was well borne. The hypochondriac pains promptly disappeared but the general symptoms were not changed. Four weeks after the operation the patient at his own request was permitted to go home and sometime later, the day is not given, he died of pulmonary embolism.

Heilborn[8] reports 2 cases of splenectomy in endocarditis ulcerosa. The first was that of a man of 31. Two years previously he had an acute attack of articular rheumatism which left him with mitral insufficiency and stenosis. The symptoms of subacute bacterial endocarditis appeared 1½ years later. The spleen was enlarged and

tender. Blood culture was negative. After splenectomy the patient made a very good recovery and returned to work. The valvular murmurs were however unchanged. Six months later the man died from cerebral embolism, having previously had an infarct in the kidney. The second case was that of a man of 27 who had had articular rheumatism, gonorrhea, cholera and lues, for which he was actively treated. From January, 1921, onward he had a continual evening fever. The spleen which was much enlarged, was removed in March; 3 weeks later the patient suddenly became worse; signs of aneurysm appeared. A massive hemorrhage killed him on August 30. Heilborn concludes that cases of endocarditis ulcerosa, endocarditis lenta and chronic sepsis are favorably influenced by splenectomy if the clinical phenomena point to a pronounced participation of the spleen. It is important, however, to do the operation early. The removal of the spleen may prevent a continuing reinfection of the heart; perhaps it acts also by stimulating the reticulo-endothelial system. In any event the experiences to date justify further resort to operation.

There are unquestionably theoretical objections to the removal of the spleen in infective states. The spleen plays an important rôle in resistance and immunity through its large content of cells of the reticulo-endothelial system which are accepted as actively concerned in phagocytosis and in antibody production. Therefore, removal of the spleen would appear to be contraindicated from the point of view of removing an organ actively concerned in resistance and immunity. Furthermore, as Krumbhaar[9] has shown, the removal of the spleen in normal animals causes a mild anemia, which however is temporary. The antianemic function of the spleen, depending perhaps upon its power to conserve iron, is readily taken over by the bone marrow and other members of the reticulo-endothelial system. The absence of stainable bacteria in the spleen of one of our cases suggests the further thought that the organ may actually destroy bacteria.

On the other hand, just as the resistance of the lymph nodes may sometimes be overcome so that they become the sites of abscess or tuberculosis, so the spleen is very commonly found to be the seat of infection during natural and experimentally produced infections. This is probably because the histologic structure of its pulp favors filtration and localization of organisms and especially of those occurring in the blood and peritoneal cavity. Furthermore, its histologic structure facilitates bacterial embolism and infarction, especially in the course of subacute bacterial endocarditis. Under the circumstances removal of the spleen may be beneficial in the way of removing a mass of secondary infection and thereby enabling the individual better to combat the primary infection.

Summary. 1. Splenectomy for subacute bacterial endocarditis is well borne even in far-advanced cases.

2. It has not so far been followed by a permanent sterilization of the blood stream in cases in which blood stream infection has existed.

3. Nevertheless, in every one of our cases life was unquestionably prolonged and made more comfortable. The physical and psychic improvement is most impressive. Even if the infectious process should continue in the heart, and it is possible that even this might be favorably affected, it seems that the general condition of the patient is improved.

4. Perhaps if the operation were done earlier in patients with palpable spleens and hearts not too badly damaged, the results might be better.

5. As death seems to be due in the majority of cases to embolism, the prevention of this complication should be taken into consideration. Nothing, we admit, may come of the attempt.

6. Treatment should not rest with splenectomy. Repeated small transfusions should be continued and bacteriophage therapy tried.

7. Splenectomy may prove to be a method of dealing with intractable forms of sepsis without discoverable focus in which splenomegaly is a prominent feature. This group, in which subacute bacterial endocarditis may be suspected but is unproved, at present promises the best results from the operation.

REFERENCES.

1. Riesman, D.: Chronic Septicemic Endocarditis With Splenomegaly—Treatment by Splenectomy, J. Am. Med. Assn., **71**, 10, 1918.
2. Sawadski: Russk. Klin., **4**, 875, 1925.
3. Wieden, L.: Ueber Milzexstirpationen und Nachuntersuchungen an Milzexstirpierten, Mitt. a. d. Grenzgeb. d. Med. u. Chir., **44**, 13, 1935.
4. Vogel, R.: Splenectomy in Blood Diseases, Deutsch. Ztschr. f. Chir., **180**, 37, 1923.
5. Nordmann, A.: Discussion, Ibid., Kongress, **45**, 240, 1921.
6. Münzer, E.: Discussion, Verhandl. d. deutsch. Kongresses f. inn. Med., **32**, 241, 1920.
7. Escudero, P., and Merlo, E. V.: Splenectomy in the Treatment of Endocarditis, Rev. de la Soc. de med. int., **1**, 361, 1925.
8. Heilborn, F.: Is it Possible to Influence Ulcerous Endocarditis or Sepsis by Extirpation of the Spleen? Med. Klin., **22**, 535, 1926.
9. Krumbhaar, E. B.: The Changes Produced in the Blood Picture by Removal of the Normal Mammalian Spleen, Am. J. Med. Sci., **184**, 215, 1932.

GOUT—A FORGOTTEN DISEASE.

By W. W. Herrick, M.D.,

PROFESSOR OF CLINICAL MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ATTENDING PHYSICIAN, PRESBYTERIAN HOSPITAL AND SLOANE HOSPITAL FOR WOMEN,

AND

T. Lloyd Tyson, M.D.,

ASSISTANT IN MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ASSISTANT PHYSICIAN, PRESBYTERIAN HOSPITAL, NEW YORK CITY.

Fashions in therapy may have some justification; fashions in diagnosis have none. Strangely enough, acute gout, one of the oldest maladies known to medicine, seems almost to have become

one of the forgotten diseases. Here is a definite clinical entity of which there is ample description and record and which in its ordinary manifestations is easy of recognition; and yet it seems to have become the fashion persistently to ignore it in the differential diagnosis of the arthritides. Is this not another example of the closing of the mind to the obvious—a fault that so seriously besets all medical diagnosis?

It may be well to recall certain historical facts about gout. First described by Hippocrates as podagra, cheiragra or gonagra, depending upon whether the toe, wrist or knee joint was involved, it was thought by him to be dependent upon the retention of humors. Galen suggested the unnatural accumulation of matters in the involved joints. Celsus advised the avoidance of corpulence in the prevention and cure. As early as the sixth century, Alexander of Tralles, a Greek physician, recommended a regimen with little meat, strict temperance, bleeding, and purging with colchicin. Rodulfe, in the thirteenth century, gave the disorder the name "gout" from the French "goutte," a drop; signifying that the poison entered the joint drop by drop. Sydenham's seventeenth century treatise on gout remains the best clinical description of the disease. Wollaston, in 1797, was the first to approach the fundamental cause of this malady when he discovered that the "chalk stones" in gouty joints consisted principally of uric acid. Garrod, in 1847, demonstrated that abnormal amounts of uric acid could be recovered from the blood of patients suffering from gout, an observation which marked one of the first chemical approaches to the study of disease. Since then a further novel contribution is Llewellyn's suggestion that, in addition to a disorder of uric acid metabolism, there is an allergic factor. This writer cites examples of patients whose gouty attacks were provoked by hives, upper respiratory infections, asthma, typhoid inoculations and even gnat bite. He also points out that eosinophilia not infrequently accompanies these attacks.

One may well ask why a disease so long recognized, so well known and in general so easy of diagnosis is frequently overlooked. Perhaps one reason is the newly awakened interest in arthritis. In the recognition and treatment of the various forms of osteoarthritis, rheumatoid arthritis and specific infectious arthritis, the possibility of a chemical arthritis seems to have been largely ignored. In his enthusiasm for the new and important facts disclosed by the recent studies in this group of disorders the practitioner seems strangely to have forgotten gouty arthritis.

And yet, from the patient's standpoint, gout is the one type of arthritis in which we have most to offer. When recognized in the early acute stages the disease can be treated successfully in prac-

tically all cases, a statement which cannot be made safely about other arthritides.

Because of the effectiveness of therapy of this disease and of the serious consequences of its neglect it may be of value to set down our own recent experiences in acute gout, at the same time pointing out specific diagnostic pitfalls and calling attention to such general errors as may lurk in diagnostic fashions.

In an office practice, limited to internal medicine, we have been impressed with the frequency of recurrent gout and with the number of cases lacking a correct diagnosis for long periods of time. During the past 12 months we have observed 6 cases of acute gout in this office. This figure, while not large, indicates that this disease is not as rare as it is ordinarily supposed to be; since arthritis of any description is a complaint of but a small minority of our patients. In comparison, at the large arthritis clinic of the Presbyterian Hospital, during the past year but 5 cases of gout have been seen. This would indicate that the disease is much more common in private than in clinic practice, probably because of the higher standard of living among private patients.

Short summaries of the 6 cases recently observed is given:

Case Abstracts. CASE 1.—Mrs. J. P., a woman aged 55, with a tendency to obesity, never had any joint trouble until September, 1934. At that time, following mild trauma to the left great toe, it became greatly swollen, tender and red. The patient was seen by several physicians, had roentgenograms made with negative findings and was finally told her condition was an arthritis. By this time the process had spread to the other great toe and to the knee and hip. Treatment having brought no benefit, she finally insisted to her physician that she had gout, stating that her mother had had similar attacks of this disease. The uric acid of the blood was found to be 7 mg. per 100 cc. No colchicin or other specific treatment was given but the patient gradually improved. She first visited us during a minor attack of podagra in January, 1935. The uric acid of the blood was then 5 mg. per 100 cc. The attack yielded to colchicin in 24 hours. Upon a regimen the patient remained symptom-free, with the blood uric acid between 3 and 4 mg. per 100 cc. In January, 1936, the patient again reported with severe pain in the lower lumbar region. In this instance it was discovered that liver extract had been prescribed for a skin condition and that 12 capsules of this substance had been taken daily. The uric acid was 5.7 mg. The pains completely disappeared 48 hours after beginning the use of colchicin, and the patient has since remained well. Further uric acid readings have not been made.

CASE 2.—Mr. W. A. M., aged 55, complained of attacks of acute arthritis in ankles, knees and great toes, at intervals, for 12 years. They were usually acute and lasted 1 or 2 weeks. With each, a newly infected tooth had been found and removed, always with eventual subsidence of symptoms. The patient took no alcoholic drinks but was overweight and plethoric. He was first seen by us in October, 1935, during an attack of what had heretofore been called arthritis. There was swelling and tenderness of the left ankle and knee, also a phlebitis of the left leg. The uric acid of the blood was 7.2 mg. per 100 cc. Following treatment by colchicin

and diet the pain subsided promptly and the uric acid gradually fell to 4.4 mg. There has been no return of symptoms.

CASE 3.—Mrs. F. R., aged 69, complained of a severe monarticular arthritis of the left knee of 4 weeks' duration. She took alcohol in moderation and had been taking liver extract by mouth. The diagnosis had been arthritis despite negative Roentgen rays of the joints. Treatment by rest and heat was without relief. Pain prevented sleep. There was no extension to other joints. We first saw the patient in April, 1935. The left knee joint was tender, swollen and red over the inner aspect, with no excess of fluid. The uric acid of the blood was 4.6 mg. per 100 cc. A diagnosis of gout was made and colchicin given. The pain disappeared in 24 hours and there has been no recurrence. In January, 1936, the uric acid was 2.5 mg.

CASE 4.—Mr. E. R., aged 56, complained of intermittent attacks of arthritis for 4 years, with free periods between. His father suffered from a similar arthritis. The joints involved had been the knees and tarsus. Some of these episodes had kept the patient in bed a month. The diagnosis had been arthritis, the treatment symptomatic, but with little apparent influence upon the usual course of the attacks. The patient was first seen by us in November, 1935, in an attack involving both knees and the left great toe. A tophus was found on the right ear. The patient was overweight and took alcohol sparingly. The uric acid of the blood was 8 mg. per 100 cc. Roentgenograms were negative. After treatment by colchicin and diet the uric acid fell to 5 mg. and the patient has thus far enjoyed the longest period free from the disease since its first appearance.

CASE 5.—Mr. J. J. C., aged 40, was first seen in 1935, complaining of pain in the right great toe, ankle and shoulder of 10 weeks' duration. There was no family history of gout and the patient did not use alcohol. Several similar attacks had occurred previously. The involved joints were found to be swollen, tender and red. The uric acid was 7.5 mg. per 100 cc. With treatment by colchicin and rest the joint symptoms subsided promptly and have no returned. The uric acid is at present 4 mg.

CASE 6.—Mr. C. M., aged 38, complained of an acute arthritis of the right ankle and metatarsal joints of 3 weeks' duration. His condition was diagnosed as arthritis, but treatment with salicylates and heat brought no relief. This patient drank heavily and noted that an overindulgence in beer aggravated the joint symptoms. On physical examination the patient was found to be overweight and with marked swelling and redness over the metatarsal and ankle joints. Roentgenograms of these joints were negative. The uric acid of the blood was 5.2 mg. per 100 cc. A diagnosis of gout was made and, following treatment with colchicin and a diet, the arthritis subsided promptly. The patient subsequently left town and further history is not obtainable.

Comment. In reviewing these cases several significant facts are apparent. All of the patients have had a similar history; namely, intermittent attacks of acute arthritis, usually in the lower extremities, lasting from 1 to 4 weeks, with intervening free intervals. In our opinion this type of history is the most important single factor in the diagnosis of gout and is found in no other type of arthritis.

A large percentage of gouty patients have a positive family history of the disease.

All of our patients have been of sthenic habitus, overweight and in the age group over 35. While gout may occur in younger people and in those of asthenic type, it is uncommon in such.

The prevalent opinion that the use of alcohol is a factor in causing the disease is not borne out by our experience. But 1 of our patients was a heavy drinker; 2 were total abstainers.

Of interest is the fact that the ingestion of liver extract in relatively large doses was a possible factor in provoking attacks in 2 cases.

In this small series the uric acid of the blood has been not less than 5 mg. per 100 cc. in all cases with acute manifestations excepting 1. This laboratory determination remains a valuable aid in diagnosis. One should remember, however, that an attack of gout may occur without a significantly elevated blood uric acid and, further, that in patients with a history of the disease, a significantly elevated blood uric acid frequently occurs without an attack of arthritis.

In all of the cases cited the radiographs were negative. This is the usual finding in the more acute types of the disease.

The usual site of the arthritis is in the lower extremities, most often the metatarsal joints; next in frequency the knee and great toe joints. It should be pointed out, however, that the upper extremities may be involved as well and sometimes alone. Tophi are infrequent. We would reiterate that these statements apply to acute and not to chronic gout. The latter presents a different picture, which needs not be described here.

Of diagnostic value in these acute cases is the dramatic alleviating or curative effect of colchicin.

Our method of treatment is the administration of this alkaloid in doses of 1 mg. 4 times on the first day of the attack, then 3 times daily thereafter until symptoms subside or diarrhea occurs. After the attack, neocinchophen (tolysin) in 0.5 gm. doses and aspirin in 0.3 gm. doses are given 3 times a day for about a week. In addition, a diet low in purins is prescribed.

Summary. 1. The frequency of acute gout especially in private practice is emphasized, as is the too common failure to recognize it.

2. The recent increased interest in the infectious and degenerative arthritides has not extended to those of chemical origin, a trend which may have promoted some diagnostic failures.

3. All cases of recurrent acute joint inflammation with intervening free intervals, especially in patients of middle age, demand careful search for a family history of gout, a study of the uric acid content of the blood and, when indicated, a therapeutic test with colchicin.

4. Tophi and positive roentgenologic signs of gout are usually absent in acute cases.

BIBLIOGRAPHY.

Duckworth, Sir D.: A Treatise on Gout, Philadelphia, Blakiston Son & Co., 1889.

Garrod, A. B.: A Treatise on Gout and Rheumatic Gout, 3d ed., London, Longmans, Green & Co., 1876.

Llewellyn, L. J.: Aspects of Rheumatism and Gout, London, William Heinemann, 1927.

Wilde, P.: Physiology of Gout, Rheumatism and Arthritis, New York, William Wood & Co., 1922.

GOUT.*

By Abraham Cohen, M.D.,

ASSISTANT PHYSICIAN TO THE PHILADELPHIA GENERAL HOSPITAL, CHIEF OF ARTHRITIS CLINICS AT PHILADELPHIA GENERAL AND JEFFERSON HOSPITALS, AND DEPARTMENT OF PUBLIC SAFETY, PHILADELPHIA, PA.

(From the Department of Public Safety and Jefferson and Philadelphia General Hospitals.)

Gout is now generally considered unimportant as a disease, and therefore the subject has been conspicuously absent in the recent literature. Gudzent and Holzmann[1] found only 76 cases of true gout in 32,089 autopsies, while McCrae[2] quotes Futcher as having discovered 59 out of 18,000 autopsies. I want to state that I have seen over 40 cases of gout during the past 5 years, and I now have 37 of these cases under my care. This suggests that the disease is more prevalent than has been supposed, and that previous criteria for diagnosis must be inadequate. When one examines the histories of these patients one soon discovers that most of them have suffered repeated attacks of gout, diagnosed "arthritis," for many years.

During the 25-year period from 1905 to 1929, it is estimated that there were approximately 414,296† admissions to the wards at Philadelphia General Hospital. In examining the records over this period, it was found that the diagnosis of gout was made only 47 times. The following is a table of the information which I have gathered from this group. Cognizance must be taken of the fact that complete studies in most instances were not available.

On the other hand, the following is a table of the cases studied from 1929 to 1935. During this period there were 146,992 patients admitted to the Philadelphia General Hospital. Among these it has been possible to make a positive diagnosis of gout 30 times. I am adding to these statistics 2 cases from the Jefferson Arthritis Clinic and 5 from my private records. It is interesting to note that 18 of my cases were from the Philadelphia Police and Fire Department.

* Read before the Medical Section of the College of Physicians of Philadelphia, May 25, 1936.

† The arbitrary number of 15,000 admissions yearly was taken from 1905 to 1911, inclusive, since the average for the subsequent 18 years was 17,000. Records for the exact number are not available.

TABLE 1.—FORTY-SEVEN CASES OF GOUT RECORDED AT THE PHILADELPHIA GENERAL HOSPITAL (1905–1929).

Age at onset:		41 to 50	10
21 to 30	7	51 to 60	1
31 to 40	8	Ages not stated	21
Duration of disease:			
1 to 5 years	10	15 to 20 years	5
5 to 10 years	5	20 to 30 years	4
10 to 15 years	3	Not stated	20
Males	44	Females	3
Colored	1 male	White	46
Positive family history	4	Not stated	22
Negative family history	21		
Lead	3	Alcoholics	10
Blood uric acid:		Elevated	8
Normal	3	Not studied	36

First blood uric acid reported by Dr. J. H. Austin, March, 1912; 7 mg. per 100 cc. blood. Normal value, 3 to 4 mg.

Joints involved:			
Great toe	24	Joints other than great toe	12
Confined to great toe	12	Polyarticular	28

TABLE 2.—THIRTY-SEVEN CASES OF GOUT (1929–1935).

Age at onset:			
10 to 20 years	4	41 to 50 years	7
21 to 30 years	5	51 to 60 years	5
31 to 40 years	15	Over 60 years	1
Duration of disease before recognition:		11 to 15 years	9
At onset	7	16 to 20 years	6
1 to 5 years	4	21 to 30 years	4
6 to 10 years	5	Over 30 years	2

Family history:		
Negative in all police and firemen		
Other cases: Negative		15
Positive		4
Onset:		
Sudden		26
Gradual		11
Attacks precipitated by:		
Appendicitis		2
Acute infection		5
Trauma		4
Tonsillectomy		1
Length of attack, three days to 10 weeks		
Blood uric acid (mg. per 100 cc. of blood):		
Average high		6.96
Average low		5.06
Highest observed		19.00
Lowest observed		3.40
3 to 4.5 mg.	6 cases	
Above 4.5 mg.	31 cases	
Length of time treated:		
3 years or over		6
2 to 3 years		8
1 to 2 years		10
3 months to 1 year		13
Monarticular		8
Polyarticular		29

From these facts the natural conclusion must be drawn, that gout is not infrequent, but that the criteria for diagnosis have been inadequate. In the 37 cases herewith reported, the following features were of diagnostic significance:

1. It occurs at any age, but mostly from 20 to 50, and often with a positive family history.
2. It is usually polyarticular.
3. It may begin as an acute or chronic disease.
4. There are attacks and remissions, the patient being pain-free during the remission, even with deformity.
5. There may be but one attack yearly or there may be many.
6. The blood uric acid is usually but not always elevated. When not elevated, the diagnosis must be made on the history of repeated characteristic exacerbations and remissions.

The following 5 case studies illustrate various features outlined above.

CASE 1.—W. W., patrolman, aged 46, height 5 feet 11 inches, weight 195 pounds, was admitted to the Philadelphia General Hospital, February 27, 1932, complaining of pain in the left knee. This attack came on suddenly, 3 days before his hospital admission. There were no prodromal symptoms except that he felt weak and exhausted for 24 hours prior to the onset. The joints were red and swollen and the patient was unable to walk.

His past history was essentially negative except that he had his first attack 13 years before, at which time both knees were involved. The attack lasted but a few days. There was no edema or redness. Since then attacks usually occurred in spring and fall of each year lasting about 6 or 7 weeks, involving several joints at a time, namely, knees, elbows, and wrists. The patient developed tophi in the cartilage of his ears, and in his elbows and right wrist about 8 years previously. He knows of nothing that might have precipitated an attack. He had received baking, "medicine," and liniment for his pain. The diagnosis of arthritis and inflammatory rheumatism was made on different occasions until his present admission, at which time the diagnosis of gout was made and confirmed.

At the hospital large tophi from both olecranon bursæ, right wrist and ears were removed. Tophi are still present in the left index finger and right metacarpophalangeal joint. He had been free from pain from January 15, 1933 to February 12, 1935.

Treatment consisted of purin-free diet and colchicin, $\frac{1}{60}$ grain, 3 times a day until the patient was well over the acute attack. He was then given the same drug, $\frac{1}{120}$ grain, 3 times daily for 1 week and a rest period for 3 weeks. Blood uric acid tests (mg. per 100 cc.) were as follows:

January 17, 1933	7.9 mg.
March 14, 1933	7.9 mg.
May 9, 1933	7.2 mg.
June 20, 1933	7.5 mg.
September 24, 1933	9.0 mg.
February 2, 1934	7.2 mg.

This patient had another attack February 12, 1935, and on questioning, admitted indiscretion in diet. He had also been drinking 2 bottles of beer daily for the previous few weeks. The blood uric acid, taken at monthly intervals, never returned to normal levels even though he was relieved of symptoms. It is to be noted that the pain did not begin in the great toe. It was deemed advisable to remove the large tophi, because ulceration is

accompanied by great suffering associated with the draining sinuses, and sometimes this lasts for many months. I believe that surgery is definitely indicated in all such cases.

CASE 2.—L. B., patrolman, aged 36, height 5 feet 7½ inches, weight 149 pounds, had his first attack of pain and swelling in the right great toe, which was preceded by itching in March, 1920. This lasted 4 or 5 weeks and was followed by pain and swelling of the entire right foot. The patient was confined to bed for 10 days, after which the foot apparently returned to normal. He has had 5 more attacks; in 1926, 1929, 1931, 1932 and 1934. These attacks occurred usually during March and subsided suddenly, with no lasting ill effects. In 1931, the pain developed after extraction of a tooth. Each attack has been less severe. The parts affected were as follows:

1920, pain and swelling in the right foot.
1926, severe pain in the left foot, great toe, and ankle. He was hospitalized 6 or 7 weeks.
1929, pain in the left foot, heel and ankle, lasting 3 or 4 days; relieved by strapping.
1931, following a cold he developed pain in the left foot, lasting 3 or 4 weeks.
1932, pain in the left foot lasting 1 month.
1934, pain in the left foot, great toe and right knee, following a cold.

The diagnosis of gout was made May 8, 1934. The blood uric acid was 8.2 mg. During the past year he was admitted to the hospital for the removal of a gangrenous appendix, and 2 days later developed an acute attack of gout, which lasted about 10 days. There are no signs of gout recognizable at present. Treatment consisted of a purin-free diet and colchicin $\frac{1}{60}$ grain, 3 times a day.

Case 2 illustrates the influence of infection in precipitating an attack of gout. It is easy to understand how a diagnosis of infectious arthritis might have been made under the circumstances.

CASE 3.—M. W., patrolman, aged 44, height 5 feet 8 inches, weight 170 pounds, was admitted to the Philadelphia General Hospital on December 1, 1933, complaining of pain in the chest, back of neck and shoulders, of 2 weeks' duration. This pain began in the left anterior chest and radiated to the scapula and back of neck. The onset of the pains was preceded by an attack of grip. The diagnosis of gout was made January 1, 1934. Blood uric acid tests were as follows:

January 2, 1934	Uric acid	8.8 mg.
	Urea nitrogen	14 mg.
January 12, 1934	Uric acid	4.8 mg.
March 27, 1934	Uric acid	4.2 mg.

No tophi were present and no signs of disease remained. He is still affected by the changes in the weather. Treatment consisted of purin-free diet and colchicin, $\frac{1}{60}$ grain, 3 times a day after meals. To date the patient has been symptom-free.

Case 3 represents another instance where the great toe was not involved, but it does illustrate the point so frequently made by textbooks that the blood uric acid returns to normal coincident with improvement in the disease. This, however, is not always true.

CASE 4.—J. Z., patrolman, aged 52, height 5 feet 8 inches, weight 155 pounds, had his first attack of pain in both ankles January 17, 1921. The

pain was more severe in the right ankle which was red and swollen, and lasted about 5 days. A diagnosis of acute articular rheumatism was made. Until March, 1932, the patient had had about 18 attacks of pain occurring usually in the fall or early spring. He knows of nothing which may have brought on the attacks; however, he noticed that the pain was aggravated if he ate meat or drank wine or beer. He was treated by his family doctor until March 24, 1927, when he was brought to the Philadelphia General Hospital, where the diagnosis of gout was made. He has been symptom-free since the above attack. This man presents typical tophi in the cartilages of his ears as well as moderate hypertension and arteriosclerosis. Blood uric acid tests were as follows:

March 28, 1933	Uric acid 7.8 mg.
March 30, 1934	Uric acid 8.8 "
	Urea nitrogen 29 "
	Blood pressure 150/100.
April 24, 1934	Uric acid 6.8 mg.
	Urea nitrogen 42 "
	Blood pressure 165/100.

Treatment consisted of a purin-free diet and colchicin $\frac{1}{120}$ grain, 3 times a day every fourth week.

Case 4 is an instance of gout with signs of renal insufficiency. There existed hypertension, arteriosclerosis, and not only a retention of uric acid, but of urea as well. Though the patient remains fairly comfortable as long as he adheres to instructions, the uric acid remains elevated and he can precipitate an attack of gout almost at will. The great toes are now involved, but this occurred fairly late in the disease.

Case 5.—J. R., patrolman, aged 58, height 5 feet $10\frac{1}{2}$ inches, weight 212 pounds, was admitted to the Philadelphia General Hospital in May, 1933, complaining of pain in the left great toe. He had had pain in this toe for about a month, but it was not severe enough to cause him to be hospitalized until the present admission. The joint was incised and wet dressings were applied for a period of 2 weeks after which the inflammation gradually subsided. He had no acute attacks of pain after the first attack.

The diagnosis of infected bunion was made until gout was suspected and confirmed by blood uric acid tests, which were as follows:

	Uric Acid.
July 25, 1933	9.4 mg.
November 14, 1933	7.7 "
January 14, 1934	4.8 "
April 10, 1934	5.2 "

Case 5 illustrates a classical attack of gout beginning with pain in the great toe, yet it was undiagnosed for many days.

Treatment. In the statistical study of the 47 cases presented from 1905 to 1929, it was found that while most cases were given up to a dram of wine of colchicum, rarely was one put on a purin-free diet. The usual dietary régime was a regular house diet. Hot magnesium sulphate solution was occasionally applied to the affected part, and salicylates were almost universally the drug of choice.

In the 37 cases herewith presented, the method of treatment was

divided into the treatment of the acute attack and treatment following the acute attack.

During the acute attack of gout, rest in bed, hot applications of saturated magnesium sulphate solution applied to the affected part, colchicin, and a liquid purin-free diet are of chief benefit. In addition supportive symptomatic treatment is given as necessary.

During the period of convalescence, the patient is put on colchicin, grain $\frac{1}{120}$, 3 times a day after meals and the purin-free diet is continued. After convalescence a purin-poor diet is prescribed and colchicin is administered grain $\frac{1}{120}$, 3 times a day after meals, for 1 week out of every 4. Blood uric acid determinations are done at monthly intervals. In cases in which the uric acid is elevated, we frequently find that this elevation continues or increases. When an elevation is discovered it becomes necessary to revert to the purin-free diet and a more active course of colchicin is instituted.

Deformities such as flat feet and contractures should be corrected as practised by the orthopedist. Infections should be cared for as one does for any other disease.

While cinchophen is efficacious in the treatment, colchicin should be used. Only one of my cases showed an idiosyncrasy to colchicin.

Treatment as described above has been highly successful. In the group now being attended, there have been but three recurrences. The patients have been treated for from 6 months to over 5 years. In each case where the disease recurred, the patient admitted indiscretions in diet or infection or trauma were the responsible factors. It is my firm belief that gout is controllable. With coöperation, the patient who would ordinarily suffer 4 to 6 attacks yearly, should no longer be troubled with this disease.

Summary. 1. A statistical study of 47 cases of gout from the admissions of the Philadelphia General Hospital, covering the period from 1905 to 1929, is presented.

2. An additional study of 37 cases covering from 1929 to 1935 is reported.

3. Attention is called to the frequency with which gout is seen in the Police and Fire Department of Philadelphia.

4. The treatment is invariably satisfactory as contrasted with other forms of arthritis.

5. Gout as a disease condition is met with fairly frequently in any large group of arthritics.

6. A revised set of diagnostic criteria are herewith submitted.

7. It is hoped that this study may lead to further studies of the incidence and treatment of gout.

REFERENCES.

1. Gudzent, F., and Holzmann, E.: Klinische und morphologische Beiträge zum Gichtproblem, Ztschr. f. klin. Med., **106**, 107, 1927.

2. McCrae, T.: Osler's Principles and Practice of Medicine, 11th ed. New York, D. Appleton-Century Co., 1935.

A FATAL CASE OF BACILLUS FRIEDLÄNDER ABSCESS OF THE PROSTATE.

By Joseph Tenenbaum, M.D.,
ATTENDING UROLOGIST, ISRAEL ZION HOSPITAL,
AND
Jacob M. Ravid, M.D.,
PATHOLOGIST, ISRAEL ZION HOSPITAL,
BROOKLYN, N. Y.

(From the Departments of Urology and Pathology, Israel Zion Hospital.)

While non-gonococcic pyemic abscesses of the prostate, whether primary or secondary, are relatively infrequent, prostatic abscess caused by the Friedländer bacillus is extremely rare. Careful search of the literature leads us to believe that our case is the first of its kind ever reported.

Case Report. A. L., white male, aged 45, was admitted to this hospital on February 20, 1935, with the complaint of "chills and fever." His past history, save for mild diabetes, was essentially negative. About 19 days before admission, he began complaining of headache and weakness. Two days later he was seized with a severe chill lasting 45 minutes, followed by rise of temperature to 104° F. He had several such attacks during the next 17 days. He also began to experience difficulty of urination.

On *physical examination* the patient appeared markedly undernourished and acutely ill; temperature 99.8° F.; pulse 80 and respiration 20 per minute. Blood pressure 94/60. The spleen was felt one finger breadth below the costal margin. The urine showed 4% glucose and a trace of acetone. Blood: 17,200 leukocytes with 76% neutrophils and 4% eosinophils. The general impression was that of bacterial sepsis from an obscure focus in a diabetic.

Course. Within 2 days, the urinary symptoms began to dominate the clinical picture. Rectal examination revealed the presence of a large semi-fluctuant mass, most pronounced in the right prostatic lobe. Seminal vesicles were markedly distended, of sausage-like configuration and appeared matted together with the mass in the prostate. The diagnosis was prostatic abscess and acute seminal vesiculitis. The patient developed a profuse urethral discharge from which B. Friedländer was isolated. As the prostatic mass seemed to shrink, this was interpreted as a sign that the abscess had ruptured into the urethra and no radical intervention was attempted. On the fourth day, however, the patient developed complete urinary retention. A total of 1200 cc. of turbid urine was obtained through the catheter, and this yielded a growth of B. Friedländer. Blood culture revealed 120 colonies of B. Friedländer per 1 cc. Cultures of the nasopharynx and stool were negative for B. Friedländer. On February 26, the patient began to show signs of meningeal involvement. Lumbar puncture yielded cloudy fluid with 660 cells per c.mm., mostly neutrophils, from which a pure culture of Friedländer bacilli was obtained. The temperature was of the septic variety, fluctuating between 98° and 106.6° F., with repeated chills. He expired the 10th day after admission.

Postmortem examination showed marked undernutrition and pallor. Fresh petechiæ were seen over the skin. The prostate and bladder, about a grapefruit in size, filled up the entire pelvis. The bladder measured 12 cm. in its longest diameter, and was filled with bloody urine. The mucosa was ulcerated and hemorrhagic. *Prostate* (Fig. 1) measured about 8 cm. in diameter, its weight with the bladder amounting to 900 gm. On section, the prostate,

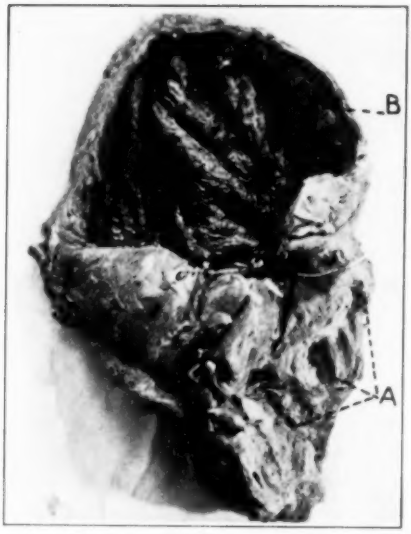


FIG. 1.—Prostate and bladder (one-third natural size) showing large abscess of prostate (*A*) and distended bladder (*B*) with hemorrhagic mucosa and markedly thickened wall.

FIG. 2.—A section of the prostate (low-power magnification) showing a large abscess cavity (*A*) filled mostly with neutrophils, a generalized round and neutrophil infiltration of the stroma with beginning fibroblastic proliferation and a few distorted acini (*B*).

seminal vesicles and vasa deferentia showed numerous honeycombed cavities, from which ill-smelling, muddy brown, purulent matter exuded. The fascia of Dénonvillier was tense but intact. The rectum, testes and urethra showed no abnormalities. Other findings of interest: lungs contained numerous minute subpleural abscesses; liver, a large subcapsular abscess in the right lobe; kidneys showed a number of small cortical abscesses, and beginning hydronephrosis. The spleen was enlarged to twice its normal size, and was soft and mushy. A pea-sized ulcer was found in the pre-pyloric region of the stomach.

On *microscopic examination*, prostate (Fig. 2) and seminal vesicles showed a widespread replacement by large abscesses made up of necrotic material with predominating neutrophil infiltration and beginning organization. A similar picture was seen in the liver, kidneys and lungs. *Cultures* from prostate, liver and lungs yielded pure growths of Friedländer's bacillus.

The final *pathologic diagnosis* was: purulent prostatitis and seminal vesiculitis with large abscess formation. Multiple pyemic abscesses in lungs and kidneys, and incipient hydronephrosis. Huge abscess of right lobe of liver. B. Friedländer septicemia. Healed tuberculosis of right lung. Acute splenic tumor. Ulcer of stomach. Coronary sclerosis and fibrosis of myocardium. Cloudy swelling of the viscera.

Discussion. Since the discovery of the organism by Friedländer in 1882, considerable change has taken place in our knowledge as to the rôle it plays in disease. At first, the organism described by him as "micrococcus" was believed to be the specific etiologic agent in lobar pneumonia. Later studies, however, have shown that the incidence of the Friedländer bacillus in lobar pneumonia averages no more than 5 to 10%,[1] the more frequent finding of this bacillus at autopsy being accounted for by pre-agonal or postmortem invasion. When found in the lungs *in vivo*, the Friedländer bacillus is either the result of a secondary infection, "contamination, or has reached the lungs from the gastro-intestinal tract, liver, bile passages or the genito-urinary tract."[2] The Friedländer bacillus, representing the large group of Bacillus mucosus capsulatus, is one of those Gram-negative bacilli which, from their habitat and pathogenicity, are related to the organisms of the upper respiratory tract; while from their biochemical and cultural behavior they are nearer to the bacteria of the gastro-intestinal tract of the coli-typhoid group. The bacillus is present in air dust, rotted potatoes, slivers, marshes and similar places, which makes contamination of the nasopharynx, gastro-intestinal and genito-urinary tracts a frequent occurrence. Etienne,[3] in an exhaustive study comprising 83 cases collected from the literature, found instances of B. Friedländer infection occurring in almost every organ of the body. The name "pneumococcus" or "pneumobacillus" is therefore a misnomer. The lesions caused by this organism range from conjunctivitis, enteritis, cholecystitis, pyelitis, abscesses of the liver and kidneys, and involvement of the internal genitalia of both male and female, to subcutaneous pyemic abscesses, endocarditis and general septicemia.

Genito-urinary Infections. In the standard textbooks of urology there is little reference to B. Friedländer as a causative agent in

genito-urinary diseases. In the current literature, however, there are a number of such reports. Montt-Saavedro,[4] Nicolaier,[5] Chiari[6] and Balog[10] reported cases of cystitis, pyelitis, pyelonephritis and kidney abscess caused by the Friedländer bacillus. Bertrand-Fontaine and Parlier[7] published a case of B. Friedländer pyelonephritis in a 5-year-old child following nasopharyngitis, with spontaneous recovery. Bernstein[8] and Barcaroli[9] reported cases of B. Friedländer epididymitis. Cain and Meyer[11] published a case of B. Friedländer infection supervening upon a latent nephrolithiasis. Brodny[12] observed a fatal case of B. Friedländer septicemia following transurethral prostatotomy.

In none of the old and recent articles did we find a case similar to ours. Cabot and Kretschmer[13] state that they have not seen such a case. Balog[10] cites a case of Sachs, of a B. Friedländer prostatic abscess without, however, indicating the source of the reference, and after a careful search no such report could be found in the literature.

It is possible that the paucity of reports of genito-urinary infections with this organism is due to the fact that pyemia and septicemia, with or without an additional mixed infection, which supervene in the majority of cases, mask the genito-urinary source of invasion. Other writers on the subject have also commented about the vagueness of the clinical picture and the lack of localizing signs in some of the obscure cases of prostatic abscess. The clinical picture in some of these patients simulated such diverse conditions as typhoid, paratyphoid, malaria, or the "grippe." Finally, there is the difficulty of positively identifying the Friedländer bacillus among its many strains and morphologic derivatives.[14] It is therefore quite probable that other cases of prostatic abscess similar to ours have been hidden or lost under the blanket diagnosis of "sepsis of undetermined origin."

Summary and Conclusions. 1. Prostatic abscess caused by the Friedländer bacillus does not appear to have been previously reported. A case of B. Friedländer prostatic abscess is here presented which eventuated in septicemia and multiple metastatic abscesses in the liver, kidneys, lungs and meninges.

2. "Sepsis of undetermined origin" or septicemia with urinary disturbances calls for a thorough investigation of the genito-urinary tract with the possibility of a hidden or masked focus in the prostate to be kept in mind.

3. The scarcity of reported cases of B. Friedländer infections of the genito-urinary tract, despite the fact that the bacillus is a more frequent invader of these organs than is commonly thought, is due partly to the existence of many strains of the organism, with mixed infection adding to the difficulty of its identification and, especially, because this organism is still being erroneously associated mainly with respiratory diseases.

REFERENCES.

1. Kliewe, H.: Epidemiologische und biologische Studien über den B. pneumoniæ Friedländer und verwandte Arten, Zentralbl. f. Bakteriol., (Abt. 1), **116**, 92, 1930.
2. Baehr, G., Shwartzman, G., and Greenspan, E. B.: The Rôle of Bacillus Friedländer in Infections, Trans. Assn. Am. Phys., **48**, 353, 1933.
3. Etienne, G.: Le pneumo-bacille de Friedländer; son rôle en pathologie, Arch. de méd. exper. et d'anat. path., **7**, 124, 1895.
4. Montt-Saavedro, R.: Zwei Fälle von Cystitis mit Befund von Diplobacillus Friedländer, Centralbl. f. Bakteriol. u. Parasitenk., **20**, 171, 1896.
5. Nicolaier, A.: Ueber einen neuen pathogenen Kapselbacillus bei eitriger Nephritis, Ibid., **16**, 601, 1894.
6. Chiari, H.: Ueber einen als Erreger einer Pyohämie beim Menschen gefundenen Kapselbacillus, Prag. med. Wchnschr., **20**, 251, 264, 274, 284, 1895.
7. Bertrand-Fontaine, Mme., and Parlier, M. R.: Pyelonéphrite à pneumobacilles de Friedländer, Arch. de méd. d. enf., **35**, 217, 1932.
8. Bernstein, E. P.: A Case of Infection of the Epididymis and Tunica Vaginalis by the Friedländer Bacillus, Am. J. Med. Sci., **126** (N. S.), 1015, 1903.
9. Barcaroli, I.: Orchiepididimite acuta da pneumobatterio di Friedländer, Gior. di batteriol. e immunol., **4**, 961, 1929.
10. Balog, P.: Pneumobazilleninfektion (Friedländer) der abführenden Harnwege mit eitriger Urethritis, Dermat. Wchnschr., **97**, 1658, 1933.
11. Cain, A., and Meyer, A.: Septico-pyohémie à bacilles de Friedländer, survenue au cours d'une lithiase réno-urétérale latente. Rapports entre le bacille de Friedländer et le colibacille, Bull. et mém. Soc. méd. d. hôp. de Paris, **49**, 79, 1933.
12. Brodny, M. L.: Fatal Case of Septicemia Due to Pneumobacillus of Friedländer Following Transurethral Prostatotomy, New England J. Med., **210**, 346, 1934.
13. Cabot, H., and Kretschmer, H. L.: Personal communications to authors.
14. Julianelle, L. A.: Distribution of Friedländer's Bacilli of Different Types, J. Exp. Med., **52**, 539, 1930.

THE TREATMENT OF GONORRHEAL ARTHRITIS WITH ARTIFICIAL FEVER.

By Robert M. Stecher, M.D.,
clinical instructor in medicine, western reserve university medical school,
and
Walter M. Solomon, M.D.,
research fellow in medicine, western reserve university medical school,
cleveland, ohio.

(From the Medical Department of Western Reserve University Medical School at City Hospital.)

Recent reports of the remarkable curative effect of artificial fever in the treatment of gonorrheal arthritis suggest that the time is not far distant when this disease will cease to be a serious factor in contributing to the number of the lame, the halt and the disabled. From the standpoint of ultimate joint function and the average duration of discomfort and disability, there is no doubt that the application of this therapeutic principle has greatly improved the outlook of patients with gonorrheal arthritis and that artificial fever constitutes the treatment of choice in such cases. Unusual individual cures have been noted by most workers in this field of therapeutics and these in a high percentage of the cases treated, but relatively little has been said of the failures. Failures there have been and as time goes on and the series lengthens, the results appear a

little less spectacular than they did in preliminary reports. After nearly 2 years' experience we are presenting the results of fever therapy in 50 cases of gonorrheal arthritis. Though the percentage of cures is not so high as has been obtained by other workers, the series is larger than any previously reported and represents the average type of patient with this form of arthritis. By giving a summary of each case in tabular form, it is hoped that the reader may arrive at his own conclusion concerning results in individual cases.

A considerable literature has appeared concerning methods of artificial fever production, the physiologic changes produced by artificial fever and the bactericidal effects of high temperatures on the gonococcus; but this has been fully reviewed in recent papers,[1,5] so that no attempt will be made to discuss it here. Concerning results of fever therapy in gonorrheal arthritis, Schnabel *et al.*[6] report 11 cases cured, 5 markedly improved and 2 moderately improved of 18 acute and chronic cases treated. Kendell *et al.*[4] report: "The ultimate average improvement in joint function in the (19) cases of acute gonorrheal arthritis was 98.4 per cent in the (12) cases of chronic gonorrheal arthritis 88.3 per cent." Hench *et al.*[3] report about 90% of their patients (16 cases) were "essentially cured or markedly relieved." These workers tabulated 9 reports from 6 groups of workers published since 1932 on the effect of fever therapy on gonorrheal arthritis. Of 33 cases mentioned, the results of only 24 could be tabulated and of these 22 (92%) were promptly and "completely relieved" or "cured." This tabulation is a composite of four different series of cases; 1 of 12 cases, 1 of 8 and 2 cases each. Such short series have the essence of preliminary reports and their reduction to statistical averages introduces the probability of considerable error. The expressed opinions concerning fever therapy in gonorrheal arthritis, such as, "Results uniformly successful in acute cases" or "Acts almost as a specific"[3] might be modified when tempered with a wider experience.

The material presented in this work consists of 50 cases of gonorrheal arthritis. Of these cases, 41 patients had joint symptoms of 10 weeks' duration or less and are, therefore, considered as acute cases. In 9 other patients, classified here as cases of chronic gonorrheal arthritis, the joint symptoms had been present for 4 months or longer. This arbitrary separation may be open to criticism, but patients in the latter group differed materially from the acute cases in that swelling was absent and pain was much more mild and even intermittent. All but 1 patient had symptoms dominated by tender heels, resulting from an inflammation of the posterior attachment of the plantar fascia. This process often interferes with locomotion and, therefore, is confused with a true arthritis of the ankles. It is seen only as a sequela of gonorrhea and often persists long after the original infection has subsided or has been cured.

The diagnosis of gonorrheal arthritis in our patients was made

by a critical consideration of the history, course and bacteriologic evidence of gonorrheal infection of the genital system and the character and type of joint disease. Classically, this occurs as a sudden, severe, extremely painful arthritis involving usually one joint and leading to rapid bone and cartilage destruction and tendon sheath inflammation. Formation of adhesions and thickening of the joint capsule result in marked limitation of joint motion or ankylosis. While such a sequence of events is suggestive of gonorrheal arthritis, it is by no means pathognomonic of this disease as the same syndrome is often seen in patients who exhibit neither suspicion nor evidence of gonorrhea. On the other hand, patients with histories of recent gonorrheal infection may have a mild migratory arthritis, limited after a short time to one joint which develops effusion, showing many pus cells and Gram-negative intracellular diplococci. A diagnosis of gonorrheal arthritis can be made with certainty only when the specific organisms are found by smear or culture in the affected joints.

According to such criteria, only 3 of this series of patients had gonococcal arthritis proven by joint culture. Of the patients with acute arthritis, all but 5 had positive urethral, prostatic or cervical smears before treatment. Three of these showed joint fluid from which gonococci were cultured (R. K., D. A. and H. B.). One of the others (M. S.) had been treated repeatedly for gonorrhea and had a urethral discharge for several days prior to the onset of arthritis. The last case (M. M.) gave a history of vaginal discharge for 4 weeks. When seen, this discharge showed many pus cells, but Gram-negative intracellular diplococci were not identified in it. The diagnosis of gonorrheal arthritis may be open to question but seemed justified on an examination of all the evidence.

Of the patients with chronic joint symptoms, only 1 had a positive smear when seen by us, but all gave definite histories of acute gonorrhea which had been adequately treated elsewhere and pronounced cured. Painful heels or arthritis had persisted since the infection. Roentgen ray films were taken in only 1 case which showed calcaneal spurs.

Apparatus and Procedure. All fever treatments were given by means of the Kettering hypertherm,* which consists of a cabinet large enough to accommodate comfortably the body of a man. The patient lies upon an air mattress resting on a built-in cart which can be withdrawn. This arrangement facilitates putting the patient into the cabinet and allows for his rapid withdrawal, if necessary. The patient's head rests upon a pillow outside the cabinet, the end of which is closed by means of a vertically sliding door. A large sliding door on each side allows for easy examination of the patient's body during the treatment, the taking of rectal temperatures and the changing of blankets which are placed over the body during part of the treatment. A compartment at the foot of the cabinet contains electrical apparatus which heats and humidifies the air and causes it to

* The Kettering hypertherm cabinets were loaned to City Hospital for clinical trial through the generosity of Mr. C. F. Kettering, President of General Motors Research Corporation, Dr. W. M. Simpson, of the Miami Valley Hospital, Dayton, Ohio, and the Frigidaire Corporation, Dayton, Ohio.

circulate. The air temperature and humidity are controlled automatically at any desired level.

The patient comes to the fever therapy department about 8 A.M. without breakfast and, after the temperature, pulse, blood pressure and weight are recorded, he receives sodium amytal (gr. vj). He then enters the cabinet nude save two boots made of several layers of outing flannel which cover the feet and lower parts of the legs, areas which are especially liable to blister. The air temperature in the cabinet at the beginning of the treatment is about 125° F. and is raised as rapidly as possible to 160° F. The humidity is maintained at about 35%. After about 1½ hours, the desired body temperature is produced and the patient is then covered with a blanket. From this time forth the cabinet air temperature is adjusted as necessary to maintain the desired fever. An electric fan plays on the patient's face, iced water or iced saline is given freely and the patient may eat ice or have ice rubbed on his face. Morphin is given hypodermically for undue discomfort or restlessness. A nurse is in constant attendance to regulate the treatment and to minister to the patient's wants. She observes and records the patient's temperature, pulse and general behavior as well as the air temperature and humidity of the cabinet at least every 15 minutes. The condition of the skin is noted to detect inflamed areas which might later develop into blisters. The nurse attends to but 1 patient at a time, and upon her intelligence, tact and judgment depends to a large extent the success of a treatment. When the treatment is terminated, the cart with the patient on it is withdrawn from the cabinet and after 1 or 2 hours the body temperature returns to the pre-treatment level. After a bath the patient is returned to the ward or may be taken home.

An attempt is made at each treatment to maintain a fever of 106° to 107° F. for at least 5 hours. If this elevation is attained rapidly, the patient is reasonably comfortable and there is no evidence of skin blisters; the period is extended to 6 or 7 hours. At the end of such a fever, patients with gonorrheal arthritis usually feel greatly improved. Pain and tenderness is markedly reduced and the range of joint motion is increased. If symptoms are not absent or do not continue to improve, fever treatments are repeated every 3 to 6 days, if possible, as long as improvement is noted. This routine is frequently disturbed and successive treatments delayed because of skin burns and blisters or painful and extensive herpes.

An important part of the patient's preparation for treatment consists in describing and explaining the procedure to him. He is told that the treatment will probably give him relief of this arthritis and his infection may possibly be cured. It is explained that the treatment is long and tedious, that the cabinet is very hot and uncomfortable, that he may suffer skin blisters and herpes, but that everything in the way of drugs and attention will be allowed to make it as easy for him as possible and that we believe he can tolerate it. Practically no one has hesitated to submit to treatment, while the few who have refused to continue have done so without resentment.

Because of the high temperatures and long treatments necessary, fever therapy in gonorrhea is much more difficult than in chronic arthritis, central nervous system lues, inflammatory eye conditions or other conditions for which it seems to be of benefit. The nervous and mental strain on the patient, the tendency to skin lesions due to thermic injury, the liability to encounter uncontrolled hyperpyrexia or circulatory collapse is increased as the temperature level is elevated.

RESULTS. So far as possible, the significant data are presented in four tables. The cases in each table are listed in order of increasing duration of arthritic symptoms. No record is stated as to the number of fever treatments given, but this may be estimated by

considering that each treatment lasts from 4 to 6 hours. The actual duration of a treatment is much longer, since the period of temperature rise is not included. Treatments are listed as "hours above 105° F." because of the difficulty at times in raising the fever to 106° F. or in keeping it there without interruption. The actual period and temperature of treatments exceed rather than fall short of the time as given. In most cases the temperature was kept as close to 107° F. as was thought to be safe.

Table 1 shows the data on 22 patients who received complete relief or cure of all joint symptoms. This means that they were free of pain and tenderness; the joints looked normal and were able to perform satisfactorily all the motions necessary in the patient's usual activity without attracting notice of an observer, although

TABLE 1.—ACUTE GONORRHEAL ARTHRITIS WITH COMPLETE RECOVERY.

	Sex.	Age.	Smear before treatment.	Duration.		Involvement.	Fever of 105° F. hr.	Remarks.
				Gon.	Arth.			
J. T.	F	22	+	1 yr.	1 wk.	Wrist	12	Pus tubes removed surgically after treatment; smear neg.
A. P.	M	30	+	1 "	1 "	Knee	8	Smear negative.
M. S.	M	37	−	2 "	1 "	Knee	5	History of repeated gonorrhea; urethritis recently; knee aspirated of 70 cc. of fluid.
W. R.	M	40	+	2 "	1 "	Knee Ankle	30	Conjunctivitis promptly relieved; smear neg.
M. K.	M	42	+	5 wk.	2 "	Ankles Elbows	5	Smear not obtainable.
J. M.	M	30	+	3 "	2 "	Knee	20	Smear negative.
J. M.	M	40	+	3 "	2 "	Knees	5	Knees tapped twice; showed Gram-neg. dip. but none intracellular.
J. B.	F	23	+	?	2 "	Knee Wrist	5	
E. W.	M	44	+	12 wk.	2 "	Ankles	10	Conjunctivitis promptly relieved.
R. S.	M	20	+	18 "	3 "	Knee	5	
F. S.	M	38	+	?	3 "	Wrist	10	Smear negative.
C. W.	M	36	+	4 wk.	3 "	Hip Knee	5	
B. B.	F	42	+	None	3 "	Wrist	5	Roentgen ray showed joint destruction.
W. D.	M	49	+	4 wk.	3 "	Knees	10	Conjunctivitis promptly relieved.
J. O.	M	22	+	8 "	3 "	Knee Heel	9	Periurethral abscess; smears became neg.
D. T.	F	24	+	4 "	3 wk.	Knee	15	
B. M.	M	32	+	1 yr.	4 "	Hip	10	
C. G.	M	21	+	4 wk.	4 "	Ankles Toes	16	
J. P.	M	22	+	8 "	4 "	Knee Wrist	7	
T. D.	M	20	+	7 "	6 "	Foot Ankle	5	
A. L.	F	5	+	?	7 "	Finger	7	Gonococcic vaginitis; Roentgen ray showed epiphyseal destruction; normal 5 wk. later.
G. L.	M	26	+	?	8 "	Knee	13	Roentgen ray shows haziness.

full anatomic motion was not always restored. One patient of special interest, but 5 years of age, had a gonorrheal vaginitis and a very tender, swollen and immovable forefinger which had been present for 6 weeks. A Roentgen ray photograph before treatment showed almost complete disappearance of the epiphysis of the proximal end of the first phalanx, whereas 5 weeks later the epiphysis was normal.

Table 2 includes 9 patients who received benefit but were not cured. In general, these patients had suffered from arthritis for

TABLE 2.—ACUTE GONORRHEAL ARTHRITIS WITH PARTIAL RELIEF.

	Sex.	Age.	Smear before treatment.	Duration.		Involvement.	Fever of 105° F.	Remarks.
				Gon.	Arth.			
K. S.	F	29	+	1 yr.	1 da.	Hip	48	First treatment within 24 hr. of first pain; developed joint damage by Roentgen ray under treatment; treatment continued for cure of infection; result: painless joint motion from complete extension to 90 degrees flexion.
A. G.	M	25	+	4 wk.	3 wk.	Foot	5	Roentgen ray showed destruction; treatment stopped for uncontrolled hyperpyrexia; foot slightly tender.
M. M.	F	16	−	16 "	3 "	Hip	20	Vaginal discharge, 4 wk.; smear: much pus, no definite gonoc.; Roentgen ray before treatment: haziness and narrowed joint space; kept in bed 4 wk. after relief of joint pain for recalcification; motion, 180 to 90 deg.; walked with slight limp.
V. S.	M	27	+	6 "	5 "	Ankles Heels	40	Gonoc. iritis promptly relieved; ankle cured; one heel tender.
L. S.	M	28	+	10 "	6 "	Ankles Wrist	29	Wrist cured; one ankle slightly tender.
W. B.	M	30	+	Denied	6 "	Wrist Hand	32	Roentgen ray before treatment showed joint destruction; complete relief of pain and tenderness.
C. R.	F	19	+	10 wk.	6 "	Knee Hip	10	Roentgen ray showed destruction before treatment; complete relief of pain and tenderness; partial motion of hip, normal of knee.
W. R.	M	..	+	9 "	7 "	Foot	7	Severe pain relieved; slight residual tenderness.
R. K.	M	23	−	10 "	8 "	Knee	8	Joint culture positive; pain had subsided; before treatment, *motion nil*, after 180 to 90 deg.

a longer time when treated than did those in the previous group. The significance of this delay is suggested by the fact that 4 patients showed Roentgen ray signs of joint damage before fever therapy was employed. That prompt fever treatment does not always protect against joint damage is illustrated by the first patient (K. S.). The onset of her arthritis was quite sudden and very painful and she had her first fever treatment, 5 hours about 106° F., within 24 hours of the first joint symptom. She had only partial relief of pain. The second treatment had to be delayed 13 days because of burns. Fever treatments in this case were continued after the joint condition became stationary in a successful effort to render her cervical smears negative for gonococci.

One patient (W. B.) showed definite destruction of bones of the wrist by Roentgen ray and had incision and drainage of suppurating tendon sheaths of the wrist before treatment. The wrist, hand and fingers were extremely tender and immovable. Fever therapy relieved the pain and tenderness completely and he regained partial mobility of the wrist, hand and fingers. This is all that could possibly be expected from any treatment, perhaps, under the circum-

TABLE 3.—ACUTE GONORRHEAL ARTHRITIS WITH DOUBTFUL RELIEF.

	Sex.	Age.	Smear before treatment.	Duration of arthritis	Involvement.	Fever of 105° F.	Remarks.
D. A.	F	18	—	1 wk.	Knee	15	Joint culture positive; Roentgen ray before showed damage; relief of pain and tenderness; motion limited to 30 degrees.
J. B.	M	..	+	1 "	Knee	6	No relief; refused further treatment.
R. S.	M	34	+	2 "	Knee	6	No relief; refused further treatment.
A. K.	F	28	+	2 "	Wrist	15	Tenderness and swelling relieved; Roentgen ray before treatment negative 1 month later; severe demineralization.
L. J.	F	43	+	2 "	Knee	15	Gradual relief of pain and tenderness.
C. L.	M	17	+	2 "	Wrist	13	Gradual relief of pain and tenderness but motion limited; developed Roentgen ray destruction under treatment.
B. K.	M	23	+	4 "	Knee	10	Refused further treatment.
J. B.	M	55	—	6 "	Hand Ankle Knee	30	Gradual relief of pain and tenderness; joint culture was positive; Roentgen ray destruction under treatment.
L. W.	M	44	+	7 "	Knee Ankle	3	Treatment discontinued because of circulatory collapse; further treatments not given.

stances. In 3 cases (K. S., C. R. and M. M.) the severity of the joint symptoms and Roentgen ray appearance suggested that bony ankylosis was to be expected, but all the patients were discharged with painless movable joints for which fever therapy seems responsible. Four patients (V. S., L. S., W. R., and A. G.) noted relief of severe pain but continued to suffer moderate and prolonged tenderness with definite limitation of motion which further fever therapy did not relieve. R. K. had marked improvement in function which further treatment might have increased but he insisted on his discharge.

Table 3 includes 10 patients who received no benefit from fever therapy. Though several of these patients showed some improvement under our observation, this was so slight in amount and so slow in appearance that it can be explained satisfactorily as the natural evolution of the disease. In contrast to the general experience, these patients noted little or no relief of pain during or directly after fever therapy. In only 2 cases (D. A. and L. J.) was there Roentgen ray evidence of joint damage prior to fever treatment, while 4 (A. K., C. L., H. D. and M. I.) developed such damage after fever therapy was started. Five patients were inadequately treated because they refused further treatment or because their reaction under therapy made further treatment seem inadvisable.

Table 4 includes 9 patients suffering with chronic manifestations of gonorrheal joint disease. The members of this group differed materially from those previously discussed. Acute pain had long since passed or had never been prominent, the joint symptoms were dominated by intermittent soreness or tenderness often relieved by exercise and without evidence of joint damage. Eight of these patients noted tenderness at the point of the heel which made walk-

TABLE 4.—CHRONIC GONORRHEAL ARTHRITIS.

	Sex.	Age.	Smear before treatment.	Duration of arthritis.	Involvement.	Fever of 105° F.	Remarks.
M. M.	M	..	—	4 mo.	Heels Ankle Hip	12	Roentgen ray shows spurs; partial relief; heels remain slightly tender.
W. C.	M	..	0	4 "	Heels	5	Complete relief.
J. K.	M	..	0	7 "	Heel Ankle	2	Complete relief.
J. S.	M	..	*	11 "	Heels	3	Complete relief.
W. W.	M	..	0	12 "	Heels	5	Complete relief.
W. B.	M	..	0	12 "	Heels	13	Partial relief.
W. P.	M	..	0	18 "	Heels	5	Partial relief.
J. G.	M	..	0	24 "	Knees Ankles	10	No benefit.
W. G.	M	..	0	24 "	Heels	1	Partial relief; stopped treatment because of extreme discomfort.

ing very difficult at times. Four patients had complete relief with a single treatment and 1 nearly complete. The latter patient was treated recently and will have further therapy. Substantial benefit was seen in another patient who suffered severe abdominal cramps during fever treatment which had to be discontinued after 1 hour of fever. Two other patients received only partial help with what was considered adequate therapy. One patient received no benefit.

Amount of Fever Therapy. A considerable variation is noted in the number of hours of fever which the patients received since some responded more rapidly than others. The longest duration of fever in a patient in Table 1 was 30 hours. Eight patients in this group required only 5 hours for complete relief and the average for the group was about 10. Of the group with partial relief, 1 patient received 48 hours of fever therapy. This was about twice as much as was indicated for joint symptoms, but treatment was continued until cervical smears became negative. The average treatment for this group was 21 hours, twice as much as in the previous one. The third group, which noted little, if any, relief, received an average of 12 hours, a figure notably reduced by the number of patients who refused further treatment or whom we preferred to discontinue. The group of chronic patients had an average of about 6 hours of fever. Treatment of 3 of these patients had to be discontinued (J. K. after 2 hours because of delirium, due to sodium amytal, J. S. after 3 hours because of persistently high pulse, and W. G. because of abdominal cramps). Despite such short treatments the first 2 of these patients received complete relief and the third partial relief. In successful cases it appears that tender heels may be relieved by fevers of short duration.

Effect on Other Symptoms. No routine attempt was made to cure the genital infection in arthritic patients. At the beginning of our experience with but one cabinet available, the press of new patients was so great that we did not feel justified in attempting to cure the genital lesion. Now with greater capacity, it is found that relatively few of our patients wish to submit to further treatments after the arthritic symptoms have subsided. Inasmuch as arthritis has been our main consideration, there has been no great pressure brought to bear on the patients. In 5 cases, definite efforts were made to effect a bacteriologic cure of the genital infection. In 1 case of arthritis, cervical smears became negative after 48 hours of fever and remained so during a 2 months' period. This patient also had tender masses on pelvic examination which disappeared. Two men without joint symptoms, 1 with prostatitis and urethritis and 1 with prostatitis and epididymitis were cured of all symptoms and discharged; shreds disappeared from the urine and prostatic smears showed only occasional pus cells without organisms during a period of 3 and 5 months that they were followed after treatment. The first patient had 15 hours of fever in 3 treat-

ments, the other 6 hours in 1 treatment. Another patient with urethritis and epididymitis received symptomatic relief and had negative smears after 10 hours of fever in 2 treatments. He unfortunately was not followed. One woman still had positive cervical smears after 40 hours of fever of about 106° F. Treatment of another patient with urethritis and epididymitis was discontinued after 1 hour because of delirium and circulatory collapse.

Of the series of arthritics, 4 had gonorrheal conjunctivitis and 1 had iritis. These conditions were relieved in every case during fever treatment for arthritis. The pain, swelling and injection usually disappeared promptly and the discharge subsided after several treatments. These patients escaped without corneal opacities. The patient with iritis was promptly relieved and now has no ocular symptoms, although adhesions did persist which are evident only after dilatation of the pupil with atropin.

Complications. Because of the severity of the treatments used, the hazards, complications and accidents encountered in the fever treatment of gonorrhea are much more common and serious than those seen in the treatment of other conditions. The patient requires larger doses of sedatives. Cyanosis occasionally develops from the use of morphin, but this is localized to the head and neck which are outside of the cabinet, the rest of the body retaining the deep flush so consistently present. Cyanosis occurs only when the patient dozes off to sleep and is promptly relieved by awakening him. The most serious effect of overdosage with morphin is diminished pulmonary ventilation, which seems to be adequately counterbalanced by the respiratory stimulation caused by heating the skin. Such respiratory stimulation at times induces sufficient hyperventilation to cause alkalosis and tetany. This occurs shortly after the patient enters the cabinet and is still without blanket covering. It is manifest by numbness and tingling of the hands and fingers and rarely by carpopedal spasm. Relief is obtained in a few minutes by lowering the cabinet air temperature slightly. Calcium gluconate intravenously is very promptly effective.

Occasionally, patients are encountered who become delirious, hyperactive or even maniacal from sodium amytal. Six grains is usually given before treatment. Inasmuch as this seems at times to be an exciting dose, an additional 3 grains is often beneficial for restlessness. If the patient becomes more restless and thrashes around in the cabinet, his temperature promptly rises to a higher level. With a temperature of 106.5° to 107° F. very little muscular activity is sufficient to produce an alarming fever in a very short time. With this additional fever deep coma may ensue, associated with a very rapid pulse, 180 to 200, a profound fall in peripheral blood pressure and a condition which appears similar to profound surgical shock save for the extreme warmth of the skin. Caffein sodium benzoate, adrenalin and 50 cc. of 50% glucose solution

intravenously cause a rise in blood pressure and slowing of the pulse. The patient gradually recovers consciousness as the temperature falls. Mild disorientation, extreme lassitude and severe headache followed later by nausea may ensue for 6 to 24 hours. Dehydration is severe and is partly due to vomiting.

The most serious experience of this kind occurred while treating a patient with prostatitis and epididymitis. The sequence of events was about as described above, except that he remained mildly disoriented and complained of a severe headache. His blood pressure varied between 60 and 80 mm. Hg. Six hours after removal from the cabinet he had a severe epileptiform seizure for about 10 minutes following which he was noted to have a facial paralysis and aphasia, which completely disappeared in about 2 weeks. Two other patients suffered similar complications in milder form, neither showing evidence of organic cerebral complications. Further fever therapy was not attempted on these patients. Two other individual treatments were discontinued because of sodium amytal delirium, but the patients later had satisfactory sessions.

It seems remarkable that the delirium of fever which is frequently seen in diseases at much lower temperatures is so rarely encountered in patients receiving artificial fever therapy. Many patients exhibit a very delicate limit of fever, varying from individual to individual, beyond which they become definitely disoriented. For example, we had 1 patient who maintained a perfectly clear sensorium at 106.8° F., but who became disoriented when the temperature rose to 107.2° F. Indeed, some patients may become disoriented with temperatures as low as 105.8° F. A few patients have remained lucid for considerable periods, from 15 to 30 minutes, at 107.5° F. We have been unable regularly to maintain the fever at such a constant level as has been described in other reports.

The ability of a patient to tolerate a definite level of fever seems to be inherent and fixed without evidence that it is increased by practice or decreased by fatigue. Individual patients have demonstrated the tolerance for fever at the same level on repeated treatments. It seems significant, also, that the patients who collapsed did so at their first treatment before or just as the desired temperature level was reached. A definite opinion has been formed by members of the department, based on experience, that if all is well by 11 A.M., no trouble is to be encountered that day.

Skin burns and blisters occur in a considerable number of patients in spite of the fact that the Kettering hypertherm contains no contact coils, electrodes or heating elements in the cabinet proper with which it is possible for any part of the patient's body to come in contact. These are the result of thermic injury of the skin due to hot air. This is not so surprising as one might think for air temperatures of 150° F. or higher may have to be maintained for 6 or 7 hours during some treatments. Certain patients tolerate this

exposure without difficulty but others, particularly those with delicately textured and fair complexioned skins, develop an intense erythema which later becomes mottled with white or ischemic areas. As such areas appear, they are massaged or kneaded gently and protected with extra pads in an effort to avert blister formation, and when such seem imminent, the treatment is terminated. Not infrequently blisters do not become evident until the following day. Patients with gonorrhea are warned of the possibility of burning as such accidents occur in about one-third of the patients.

As a rule, burns are only of the first degree and heal without scars, but it is desirable to avoid them for they necessitate curtailing the treatment or delaying the following one. Certain areas of the skin are particularly prone to blister. The toes, feet and lower legs are protected at all times by outing flannel boots and, therefore, cause very little trouble. Skin, where it is stretched over bony prominences such as the anterior-superior spines of the ilia and lower border of the ribs, is especially vulnerable as is that covering abdominal scars or pendulous breasts. Other parts where burns develop include the anteromedial aspects of the thighs, across the upper chest and the anterior aspects of the upper arms.

Herpes labialis develops in about one-third of the patients and frequently is extensive, involving the lips and skin about the mouth and chin, the labial portion of the buccal mucosa but rarely the mucosa of the hard palate. It usually becomes evident from the third to the fifth day following therapy, lasts about 5 days, invariably heals without leaving scars and occurs only after the first treatment.

The most common difficulty of patients with gonorrhea after fever treatments include nausea, vomiting and anorexia. Most patients notice nausea directly after treatment which may persist for 12 to 24 hours. Vomiting may occur upon removal from the cabinet, but usually is delayed until the patient is moved to the ward or gets up to go home. It may occur after supper if this is attempted on the treatment day. Occasionally patients are hungry and eat well at supper time, but many lack all interest in food until the following noon. They are urged to eat as soon as they feel a desire for food.

RATIONALE. The effectiveness of high temperatures as a gonococcocide has long been recognized and innumerable examples of the curative effects of severe fever from spontaneous disease upon preëxisting gonococcal infections have been reported in the literature.[5,7] It remained for the work of Carpenter[5,8] and his associates to demonstrate laboratory confirmation of this observed clinical fact. By *in vitro* experiments with 130 different strains of gonococci, they found it required from 6 to 27 hours in an incubator at 106.5° F. for complete sterilization of the various cultures. They noted further that slight reductions in incubator temperatures

resulted in a marked increase in the time required for sterilization. They have evidence to suggest that the gonococcus becomes more heat-resistant with repeated non-lethal exposure to high temperatures. These workers report that 11 patients with gonorrhea, who were given a single fever treatment of 106.5° F. maintained for a period equal to the thermal death time of their particular strain of the gonococcus, noted an immediate subsidence of all symptoms and had a bacteriologic cure. The fact that 9 other patients noted similar results with fever treatment of from one-fourth to three-fourths of the thermal death time suggests that bodily mechanisms of defense often are called into action to produce a cure.

In view of the above facts, a study of the cases here reported indicates that it is extremely unlikely that the thermal death time was equalled in many cases, even though joint symptoms were controlled. In only a few cases does it seem likely that the genital focus of infection was cured. This suggests that metastatic gonorrheal infection in joints is more vulnerable to sterilization from direct heat or defense mechanisms of the body than is the primary genital infection.

In attempting to analyze the value of artificial fever in the treatment of gonorrheal arthritis, reference must be made to the expectancy of spontaneous remission in the disease. We are not aware of statistical studies on this subject, but we are convinced that a significant proportion of cases attain a satisfactory result without medical intervention. We have no idea what this proportion may be. Anyone familiar with this disease can recall even severe cases which recovered following only bed rest or joint protection during the acute stage. In a study of synovial fluid, Myers *et al.*[9] state that 25% of 33 patients became well following gonococcal arthritis and noted a direct relationship between prognosis and cell count of the synovial fluid. These cases were of sufficient severity to have fluid in the joints which could be removed by tapping. No mention is made of the therapy employed.

The experiences recorded in this paper have convinced the authors that fever therapy constitutes a practical, safe and satisfactory method of treatment in gonorrheal arthritis, producing cure or relief for a high percentage of patients treated and reducing markedly the period of disability and discomfort attendant with this disease. The treatment is highly technical and not to be undertaken without careful supervision by a trained personnel. It is not without hazard and disagreeable complications seem unavoidable.

Summary. Fifty cases of gonorrheal arthritis, treated with artificial fever (105° to 107° F. from 1 to 48 hours) in the Kettering hypertherm are reported. Of these patients, 26 (54%) were relieved of all joint symptoms, 11 (22%) received benefit, while 13 (26%) were not helped. The apparatus and procedures are described in detail, mention is made of the common complications encountered. The rationale of fever therapy in gonorrheal arthritis is discussed.

REFERENCES.

1. Simpson, W. M.: Artificial Fever Therapy: Report of Researches at Miami Valley Hospital, Proc. Staff Meet. Mayo Clin., **9**, 567, 1934.
2. Desjardins, A. U., Stuhler, L. G., and Popp, W. C.: Fever Therapy for Gonococcic Infections, J. Am. Med. Assn., **104**, 873, 1935.
3. Hench, P. S., Slocumb, C. H., and Popp, W. C.: Fever Therapy: Results for Gonorrheal Arthritis, Chronic Infectious (Atrophic) Arthritis, and Other Forms of "Rheumatism," Ibid., p. 1779.
4. Kendell, H. W., Webb, W. W., and Simpson, W. M.: Artificial Fever Therapy of Gonorrheal Arthritis: Report of 31 Cases, Am. J. Surg., **29**, 428, 1935.
5. Carpenter, C. M., Boak, R. A., Mucci, L. A., and Warren, S. L.: Studies on Physiologic Effects of Fever Temperatures; Thermal Death Time of Neisseria Gonorrhœæ *in Vitro*, With Special Reference to Fever Temperatures, J. Lab. and Clin. Med., **18**, 981, 1933.
6. Schnabel, T. G., and Fetter, F.: Fever Therapy in Gonorrheal Arthritis and Chorea, Ann. Int. Med., **9**, 398, 1935.
7. Quoted by Desjardins *et al.*, and Carpenter *et al.* See 2 and 5.
8. Boak, R. A., Carpenter, C. M., and Warren, S. L.: The Thermal Death Time of 130 Strains of Neisseria Gonorrhœæ: The Basic Principles for the Cure of Gonococcal Infections by a Single Fever Treatment: Fifth Annual Fever Conference, Dayton, Ohio, May 2 and 3, 1935.
9. Myers, W. K., Keefer, C. S., and Holmes, W. F., Jr.: The Characteristics of Synovial Fluid in Gonococcal Arthritis, J. Clin. Invest., **13**, 767, 1934.

THE EFFECT OF INTRAVENOUS INJECTIONS OF SUCROSE SOLUTION (50%) ON THE CEREBROSPINAL FLUID PRESSURE, THE BLOOD PRESSURE AND CLINICAL COURSE IN CASES OF CHRONIC HYPERTENSION.*

By Francis D. Murphy, M.D.,
PROFESSOR OF MEDICINE, MARQUETTE UNIVERSITY,

R. A. Hershberg, M.D.,
RESIDENT PHYSICIAN, MILWAUKEE COUNTY GENERAL HOSPITAL,
AND
Alex M. Katz, M.D.,
RESIDENT PHYSICIAN, MILWAUKEE COUNTY GENERAL HOSPITAL.

(From the Department of Medicine, Marquette University and the Medical Clinic of Milwaukee County General Hospital.)

The relationship between arterial hypertension and increased cerebrospinal fluid pressure has been noted by many investigators since Traube's observations in the year 1871.[1] Yet a review of the literature on the subject up to recent times shows that there was no unanimity of opinion concerning the correspondence of the pressure changes in the two systems. Recently, however, Shelburne, Blain, and O'Hare[2] have pointed out that there is an almost constant association between an excessively high diastolic blood pressure, and an increase in the spinal fluid pressure. They have shown further that there is a relationship between the cerebrospinal fluid pressure, a high diastolic blood pressure, and papilledema. They found in-

* Presented at the Eighth Annual Meeting of the Central Society for Clinical Research, Chicago, November 2, 1935.

creased intracranial pressure more often associated with high diastolic blood pressure but felt that both were probably the results of some common factor, neither caused by the other. The results of their study were in harmony with those published later by Pickering.[3] He concluded that there is a relationship between high diastolic blood pressure and high cerebrospinal fluid pressure and suggested that the former is one of the factors determining the latter.

From clinical observations it may be concluded that in patients with excessively high blood pressures the most aggravating symptoms often refractory to treatment are those not of renal failure, but of edema of the brain and increased intracranial pressure. The headache, nausea and vomiting, vertigo, and the disturbances of vision associated with papilledema are evidences of increased intracranial pressure and are often the prodromes of convulsive seizures. In such cases spinal fluid pressure is usually considerably elevated and commonly the diastolic blood pressure is 130 mm. of Hg. or above. Autopsies in such cases show the brain is edematous, pale, and bloodless. Although there are other theories concerning the production of these symptoms Volhard[4] prefers to consider edema of the brain as the most important factor.

For the relief of intracranial pressure of nephritis and of hypertension, several methods have been employed. For example, in 1908, Cushing and Bordley[5] performed subtemporal decompression in such cases for the reduction of cerebrospinal fluid pressure. They noted marked improvement in the general condition of the patient and particularly an improvement in the visual acuity. Lumbar puncture has been used for relief of symptoms but it has been shown by Shelburne, Blain, and O'Hare,[2] and by such authors as Volhard[4] and Blackfan and Hamilton[6] that serious unfavorable results may follow spinal puncture. The release of the pressure may cause the medulla oblongata to become pressed into the foramen magnum and lead to respiratory failure and death.

When it was discovered experimentally by Weed and McKibben,[7] in 1919, that hypertonic salt solution and hypertonic glucose solution given intravenously would cause a reduction of brain fluid volume and spinal fluid pressure, the clinical application of this discovery soon followed. The first clinical report was made by Haden[8] who used a 40% solution of glucose for the treatment of intracranial pressure in cases of meningitis. The results were favorable. The value of these hypertonic solutions was more greatly appreciated by surgeons than by internists and their chief clinical use has been in the field of surgery in the treatment of increased intracranial pressure produced by acute and chronic lesions within the cranial cavity itself.

Hypertonic saline solutions were shown to reduce spinal fluid pressure but later were found to be toxic by Browder[9] who claimed there was danger in the use of them. Blackfan and Hamilton[6]

employed magnesium sulphate for the reduction of intracranial pressure. Fay[10] advocated giving magnesium sulphate by mouth for the same purpose in treating patients with intracranial lesions. Hypertonic glucose solution has been widely used and advocated for this purpose, especially by Peet[11] who used intravenously 50% solution daily. The value of hypertonic glucose solution in such cases has been questioned by several authors among whom are Milles and Hurwitz,[12] Jackson, Kutsunai, Leader and Joseph.[13] In their opinions the reduction of cerebrospinal fluid pressure with hypertonic glucose solution is transient and within a period of 3 hours a secondary rise above the basic level occurs. They concluded that the use of such a measure carries an obvious danger.

Bullock, Gregersen and Kinney,[14] in an experimental study, compared the effects of intravenously injected glucose, sodium chlorid, and sucrose upon the cerebrospinal fluid pressure. They found that the intravenous injection of 50% glucose solution and 30% sodium chlorid reduced the spinal fluid pressure for 2 to 3 hours; the pressure then rose above the control level. Hypertonic (50%) sucrose injected intravenously reduced the spinal fluid pressure in dogs for from 5 to 8 hours without causing a secondary rise exceeding the initial pressure. They explain that this effect is because of the increased osmotic pressure of the blood. It remains in the blood longer than glucose or sodium chlorid solutions and has a more prolonged effect because it is not broken down or utilized as is glucose nor on the other hand is it stored in the tissues as is sodium chlorid. Pronounced diuresis follows sucrose injections and this eliminates the sucrose as well as fluid withdrawn from the tissues. The excretion and utilization of sucrose when injected intravenously were studied by Keith and his associates.[15] They found that in normal persons 97 to 98% of sucrose was excreted in the urine in 24 hours. In contrast to the rapid excretion of sucrose by the normal person, they found that in patients with renal insufficiency there was a delay in excretion. In spite of the delay the total amount recovered was 88 to 99%.

Recently Masserman[16] presented evidence to show that when hypertonic solution of glucose in effective amount and concentration is given intravenously for the purpose of reducing intracranial pressure the reduction of cerebrospinal fluid pressure may be followed by a period of increased intracranial pressure and by a number of unfavorable signs and symptoms. In an attempt to find a nontoxic substance whose osmotic action would not be complicated by these unfavorable sequelæ he investigated the effects of intravenous hypertonic solution of sucrose. He concluded that a 50% solution of sucrose was satisfactory for clinical use and that as high as 500 cc. of this solution may be given intravenously without any toxic or other untoward symptoms. The desired reduction in intracranial pressure was obtained and the effect was greater and more prolonged than that of glucose solution. Masserman noted that a

marked diuresis followed the use of sucrose solution. He suggested the use of this measure to reduce intracranial hypertension in medical and surgical cases.

Clinical Observations. With these observations on cerebrospinal fluid pressures in hypertensives in mind, and in view of the favorable effects of hypertonic sucrose solution in other types of cases, we were led to attempt to obtain temporary relief of symptoms of intracranial pressure of hypertensives by daily intravenous injections of hypertonic sucrose solution. The purpose of this report is to present the effects of giving patients with hypertension 50% sucrose solution intravenously. Especial attention is given to the influence of the injections upon the spinal fluid pressure, blood pressure, eye-ground changes, and the clinical course of the disease. In all, 21 cases of hypertension were selected: 10 had essential benign hypertension, 7 had malignant hypertension, and 4 were cases of chronic glomerular nephritis. Spinal fluid pressure readings were made with an Ayer water manometer. A reading of less than 200 mm. was considered normal.

TABLE 1.—CLINICAL DATA IN 10 CASES OF BENIGN HYPERTENSION.

Case.	Age, yrs.	Blood pressure, mm. Hg.	CSF pressure, mm. water.	Papill-edema.	Renal failure.	Cardiac failure.
1	48	190/100	125	0	Mild	Advanced
2	38	180/116	90	0	0	Moderate
3	57	200/110	215	0	0	Mild
4	44	200/145	205	+	Mild	Advanced
5	30	196/134	250	0	0	Mild
6	53	230/100	250	0	Mild	Advanced
7	28	240/116	130	0	Severe	Advanced
8	49	224/120	185	0	0	0
9	51	210/125	178	0	0	Mild
10	48	215/110	195	0	0	0

In Table 1 the clinical features of the group of benign hypertensives are tabulated. It is seen that no decided increase in intraspinal pressure was present in most cases. Exceptions, however, are seen in Cases 5 and 6. Although the diastolic blood pressures and cerebrospinal fluid pressures are elevated, no papilledema was found. These cases show that no constant relationship exists between high diastolic blood pressure and increased cerebrospinal fluid pressure.

TABLE 2.—CLINICAL DATA IN 7 CASES OF MALIGNANT HYPERTENSION AND IN 4 CASES OF CHRONIC GLOMERULAR NEPHRITIS.

Case.	Age, yrs.	Diagnosis.	Blood pressure, mm. Hg.	CSF pressure, mm. water.	Papill-edema.	Renal failure.	Cardiac failure.
11	37	Malig. hyper.	200/140	350	++	Advanced	Advanced
12	56	Malig. hyper.	200/130	250	++	Mild	Advanced
13	43	Malig. hyper.	250/140	250	++	Mild	Advanced
14	48	Malig. hyper.	182/120	275	++	Moderate	Advanced
15	45	Premalig. hyper.	210/125	350	0	Moderate	Moderate
16	39	Malig. hyper.	230/190	200	++	Advanced	Advanced
17	58	Malig. hyper.	260/140	200	++	Mild	Advanced
18	40	Chr. glom. nephr.	240/150	150	++	Advanced	Advanced
19	30	Chr. glom. nephr.	180/110	250	++	Advanced	0
20	28	Chr. glom. nephr.	180/100	200	++	Advanced	Advanced
21	38	Chr. glom. nephr.	210/150	350	++	Advanced	Mild

In Table 2 are placed the cases of malignant hypertension and of chronic glomerular nephritis. With few exceptions there is a decided increase in cerebrospinal fluid pressure. The high diastolic blood pressure and renal failure seem to correspond to the elevation of spinal fluid pressure and papilledema. An exact correspondence, however, is lacking as seen in Case 15 where no papilledema is present although the spinal fluid pressure is 350 mm. of water. By the exceptions in these cases it is evident that there is no constant relationship between diastolic blood pressure and increased cerebrospinal pressure, for diastolic pressure may be constantly elevated yet there is no increase of spinal fluid pressure.

TABLE 3.—SUMMARY OF DATA SHOWING THE CORRELATION BETWEEN ARTERIAL HYPERTENSION AND INCREASED CEREBROSPINAL FLUID PRESSURE.

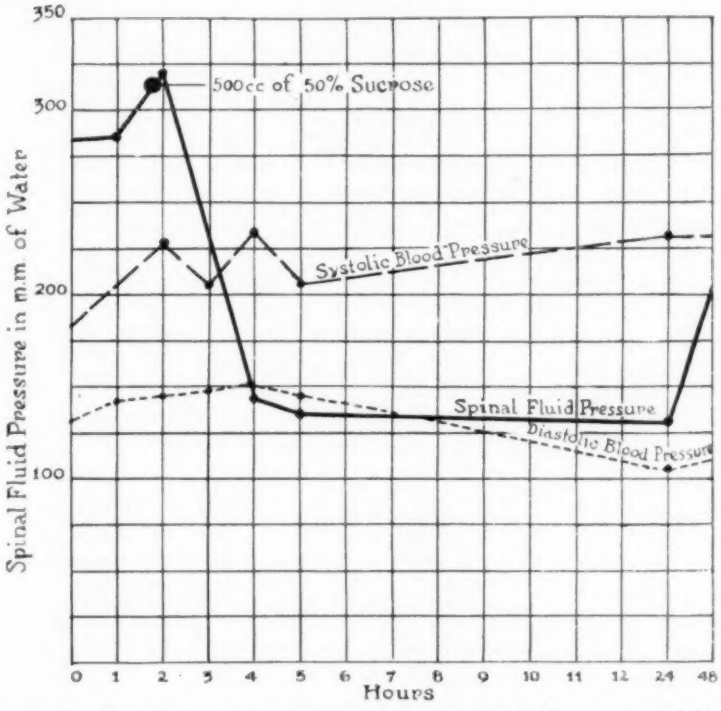
No. of cases.	Average systolic blood pressure, mm. Hg.	Average diastolic blood pressure, mm. Hg.	CSF pressure.	Number systolic above 220.	Number diastolic above 130.
7	214	112.9	Below 200 mm. water	3 (43%)	1 (14.9%)
14	210	131.0	Above 200 mm. water	4 (28%)	7 (50%)

Referring to Table 3 a summary is given showing the correlation between the elevation of cerebrospinal pressures and high diastolic blood pressures. Of 14 cases with spinal fluid pressure of 200 mm. of water and above, 7 had a diastolic blood pressure of 130 mm. of Hg. or above. Of 7 patients with cerebrospinal fluid pressure below 200 mm. of water, 1 (14.9%) had a diastolic blood pressure above 130 mm. of Hg. and 3 (43%) had a systolic blood pressure above 220 mm. of Hg. In Case 18 there is a diastolic pressure constantly over 130 mm. of Hg. yet the spinal fluid pressure is normal. The most satisfactory results occur in the treatment of patients with malignant hypertension. The usual response obtained is shown in Graph 1.

Method of Procedure. On the morning of the study, breakfast is withheld and the patient sedated with a drug such as sodium luminal. The mean blood pressure and pulse rates are established by readings every 15 minutes. An indwelling spinal tap needle is placed in the spinal canal and the basic spinal fluid pressure is established. Then the patient is given 300 to 500 cc. of 50% sucrose solution and the blood pressure, spinal fluid pressure, and pulse rates are followed every 15 minutes. This procedure is carried on as long as the patient is able to tolerate comfortably the indwelling spinal tap needle; this is a period usually from 2 to 5 hours.

When the solution is given to patients with benign hypertension the spinal fluid pressure drops from 80 to 100 mm. below the basic level. Within 5 to 12 hours it gradually returns to normal. No unfavorable symptoms develop, such as phlebitis, headache, sweating, or distress of any kind. A decided diuresis is noted in each case. After 2 hours diuresis sets in and within 20 hours as much as 2100 to 3500 cc. are excreted.

Our interest was particularly focussed upon the 7 cases of malignant hypertension and the 4 cases of chronic glomerular nephritis. In 10 of these the spinal fluid pressure ranged from 200 to 350 mm. of water. Diastolic blood pressure persisted above 130 mm. Hg. and choked disks were present



GRAPH 1.—The effect of intravenous sucrose on spinal fluid pressure and blood pressure in malignant hypertension.

in all except one case. Within 3 hours following the injection, spinal fluid pressure was reduced to a level of 40 mm. of water. Within from 3 to 24 hours, a gradual rise to basic level occurred.

In every case there was a prompt diuresis within 2 hours, although this was less pronounced in the nephritics than in the others. Headache, restlessness, nausea and vomiting were relieved. In no case was there a pronounced deviation of blood pressure from the original level. In no case were there any unfavorable effects of the treatment and the clinical condition of the patient seemed to be improved.

Comment. Patients with nephritis and those with hypertension of the malignant form frequently have signs and symptoms of increased intracranial pressure. The most distressing symptoms in this period are closely related to and probably caused by the increase of intracranial pressure. Uremic convulsions are associated with a very high diastolic blood pressure and an increased intracranial pressure. In the management of such cases it is desirable to reduce the spinal fluid pressure, in order to forestall convulsions and relieve symptoms and to promote diuresis for prevention of genuine uremic coma. From the experimental and clinical experiences of other workers, it is evident that a substance is desirable which will accomplish these results when given intravenously. To be of clinical value such a solution should have the following properties: 1, it

must be non-toxic when given in large doses of high concentration; 2, it must reduce spinal fluid pressure, sustain the low pressure for hours or days and must not cause a secondary rise above the basic level; 3, it should produce a prompt diuresis for the elimination of fluid is necessary for the reduction of spinal fluid and also for the prevention of retention of nitrogen products. According to the investigative work of Bullock, Gregersen, and Kinney[4] and of Masserman,[17] sucrose fulfills these conditions. It must be kept in mind that unless caution is used the intravenous injection of any hypertonic solution may be followed by unfavorable reactions. In cases of hypertension the heart may become embarrassed by the sudden increase of fluid in the vascular system. It may be noted that in our work we have used doses as large as 300 to 500 cc. of 50% solution intravenously without untoward effects. We believe it must be given slowly and the injection stopped at the first sign of disagreeable effects. To emphasize the non-toxic effects of sucrose, Bullock received 3 gm. per kg. body weight (432 cc. 50% solution) intravenously in 2 hours. There was no symptom except thirst, which was relieved on drinking water.

The effects of this therapeutic measure in our clinical work conforms fairly closely with those obtained by the above-mentioned research students. The prompt reduction of spinal fluid pressure without a subsequent secondary rise above the basic level, the relief from grave symptoms as headache, vomiting and vertigo, the prompt diuresis and the freedom from toxic reactions were features that encouraged us to apply this method in our work and to report the results. One of the chief recommendations of sucrose solution is that on repeated injections, no unfavorable results were noted in any case.

Summary. 1. A study is reported of the cerebrospinal fluid pressure and blood pressure of 21 cases of chronic hypertension.

2. There is not an exact correspondence between an elevation of cerebrospinal fluid pressure, papilledema and an excessively high diastolic blood pressure, but there is a close association between the three in most cases.

3. The effects of administering a 50% solution of sucrose intravenously are given. When 300 to 500 cc. of the solution are injected there is a prompt and prolonged reduction of spinal fluid pressure followed by a gradual return to the basic level in from 8 to 12 hours.

4. A prompt and profuse diuresis follows the injection; it begins about 2 hours after the injection and continues usually for 6 hours.

5. In this series of cases no unfavorable results were noted following the use of sucrose solution. Clinically, the patients were improved.

6. Intravenous injection of hypertonic (50%) sucrose solution is effective in reducing the elevated spinal fluid pressure that occurs in advanced arterial hypertension; diuresis is established and the aggravating symptoms such as headache, vomiting, vertigo, twitching, and dizziness, have been relieved.

REFERENCES.

1. Traube, L., quoted by Bartels, C.: in Ziemssen's Cyclopedia of the Practice of Medicine, New York, William Wood & Co., **15**, 121, 1877.
2. Shelburne, S. A., Blain, D., and O'Hare, J. P.: The Spinal Fluid in Hypertension, J. Clin. Invest., **11**, 489, 1932.
3. Pickering, G. W.: The Cerebrospinal Fluid Pressure in Arterial Hypertension, Clinical Science incorporating Heart, **1**, 397, 1934.
4. Volhard, F.: in Handb. d. inn. Med., G. von Bergheim und R. Staehlin, Berlin, Julius Springer, **6**, Pt. 2, 551, 1931.
5. Cushing, H., and Bordley, J.: Subtemporal Decompression in a Case of Chronic Nephritis with Uremia; with Especial Consideration of the Neuroretinal Lesion, Am. J. Med. Sci., **136**, 484, 1908.
6. Blackfan, K. D., and Hamilton, B.: Uremia in Acute Glomerular Nephritis; Cause and Treatment in Children, Boston Med. and Surg. J., **193**, 617, 1925.
7. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injections of Solutions of Various Concentrations, Am. J. Physiol., **48**, 512, 1919.
8. Haden, R. L.: Therapeutic Application of the Alteration of Brain Volume by the Intravenous Injection of Glucose, J. Am. Med. Assn., **73**, 983, 1919.
9. Browder, J.: Dangers in Use of Hypertonic Solutions in Treatment of Brain Injuries, Am. J. Surg., **8**, 1213, 1930.
10. Fay, T.: Administration of Hypertonic Salt Solutions for Relief of Intracranial Pressure, J. Am. Med. Assn., **80**, 1445, 1923.
11. Peet, M. M.: Reduction of Increased Intracranial Pressure by Intravenous Administration of Glucose and Hypertonic Ringer's Solution, Ibid., **84**, 1994, 1925.
12. Milles, G., and Hurwitz, P.: Effect of Hypertonic Solutions on Cerebrospinal Fluid Pressure, with Special Reference to Secondary Rise and Toxicity, Arch. Surg., **24**, 591, 1932.
13. Jackson, H., Kutsunai, T., Leader, L. O., and Joseph, L. D.: Effects of Hypertonic Dextrose Solutions on Intracranial Pressure in Acute Cranial Injuries, J. Am. Med. Assn., **100**, 731, 1933.
14. Bullock, L. T., Gregersen, M. I., and Kinney, R.: The Use of Hypertonic Sucrose Solution Intravenously to Reduce Cerebrospinal Fluid Pressure Without a Secondary Rise, Am. J. Physiol., **112**, 97, 1935.
15. Keith, N. M., Wakefield, E. G., and Powers, M. H.: The Excretion and Utilization of Sucrose When Injected Intravenously in Man, Ibid., **101**, 63, 1932.
16. Masserman, J. H.: Effects of Intravenous Administration of Hypertonic Solutions of Dextrose, with Special Reference to Cerebrospinal Fluid Pressure, J. Am. Med. Assn., **102**, 2084, 1934.
17. Masserman, J. H.: Effects of Intravenous Administration of Hypertonic Solution of Sucrose with Special Reference to Cerebrospinal Fluid Pressure, Bull. Johns Hopkins Hosp., **57**, 12, 1935.

A CASE OF CEREBRAL DEGENERATION WITH ENCEPHALOGRAPHIC STUDY EIGHT YEARS AFTER COMMON CAROTID LIGATION.*

By Herman Wortis, M.D.,

RESIDENT NEUROLOGIST, BELLEVUE HOSPITAL, NEW YORK CITY.

(From the Department of Neurology.)

Since Benjamin Travers first ligated the common carotid artery for the treatment of pulsating exophthalmos, this condition and its treatment have continued to interest the medical profession. Dandy, Matas, Kolodny, deSchweinitz and Holloway, Fuchs and others have studied the various therapeutic measures aimed at curing this condition.

* Presented at the New York Academy of Medicine, Meeting of the New York Neurological Society, December 3, 1935.

The following case is of interest because it demonstrates in a graphic manner the brain damage which may result from ligation of the common carotid artery.

Case Abstract. N. Q., a trained nurse, aged 57, entered this hospital on July 27, 1935, in a disturbed state. She was confused, disoriented as to time and place, showed gross defects of memory and intellect, and, in general, her condition was such as to make adequate contact impossible. She was quieted with sedatives, and the following history (for which I am in great part indebted to Dr. De Wayne Hallett) was obtained.

On November 1, 1926, the patient had been in an automobile accident. She bumped her head against the windshield but the only obvious injury was a laceration over the left eye. There was no loss of consciousness and the patient was able to return to work. Twelve days later her left eye became discolored and it began to protrude slightly. One month after the accident, she began to complain of noises in her head; she said they were like the swish of waves on the shore. Meanwhile the patient became more and more irritable, saying that the noise in her head was driving her mad. Roentgen films of the skull were reported as normal. She visited various specialists, none of whom was able to determine the cause of the patient's complaints. Seen for the first time by Dr. De Wayne Hallet 63 days after the accident, the condition was recognized as one of pulsating exophthalmos —probably due to a traumatic carotid-cavernous sinus aneurysm. The following characteristic triad was noted: (1) The left eye could definitely be felt to pulsate when the slightest pressure was put on the eyeball. (2) There was measurable exophthalmos of the left eye. (3) There was a subjective and an objective bruit. The latter could be heard all over the left side of the head. It was also noticed that the bruit stopped when the left internal carotid artery was compressed.

The patient was put to bed and 27 days later (90 days after the accident) under ether anesthesia the left common carotid artery was ligated by Dr. G. W. Roberts. The immediate effects were a complete cessation of the bruit, a right hemiplegia and total aphasia. Sensation was apparently not tested at that time.

The bruit recurred 14 days later in a light blowing form audible only at the outer angle of the left orbit. It ceased on carotid compression. On the 133d postaccident day, the left superior ophthalmic vein was ligated. Following this second operation the bruit stopped but the patient progressively lost vision in the left eye, so that by September, 1927, she could only perceive light in that eye.

Her neurologic examination at the time of her Bellevue Hospital admission revealed the following: There was about 3 mm. of exophthalmos in the left eye. The left pupil was larger than the right and reacted very poorly to light on direct stimulation—its consensual reaction was good. The left nerve head was pure white; the arterioles were very thin and the veins appeared collapsed as compared to the right eye. Her visual acuity was 16/20 in the right eye; she could only perceive light with the left eye. The visual field of the right eye was well within normal limits. She had a right hemiparesis, including the lower face with associated muscular atrophy. Her gait was typically hemiplegic. There was a downward drift of the outstretched right hand which was markedly accentuated when she closed her eyes. The deep reflexes were hyperactive on the right side and the right abdominal exhausted quickly. There was a right Hoffman sign but no Babinski. Sensory examination revealed a hypesthesia and hypalgesia to all forms of sensation—most marked peripherally in a glove and stocking fashion. She had completely lost position sense on the right side. Her right hand was asteriognostic. Both extremities on the right side showed

FIG. 1.—Anteroposterior view: Showing the marked dilatation of the anterior horn of the left lateral ventricle with an increase in the markings over the surface of the left cortex.

FIG. 2.—Posterio-anterior view: Showing the dilatation of the posterior horn of the left lateral ventricle.

FIG. 3.—Right lateral view: Showing the dilated left lateral ventricle.

trophic edematous changes, most marked peripherally. She understood perfectly the spoken and written word. Her speech was slow and when she became tired or confused she developed a typical anomia which was not present at any other time.

No bruit could be hard anywhere over the head.

Her psychiatric survey is of interest. The patient has shown marked intellectual impairment since operation. She is no longer able to carry on her duties as a housewife and is almost completely dependent on her children. She has been picked up on street cars, wandering aimlessly about and completely amnesic. Her attitude toward her children has changed. She has become very demanding and irritable. Her daughter states that the patient has attempted suicide on two occasions—"never with any serious intent, but merely to attract attention to herself." Her mood during her hospital stay varied from that of a very coöperative and appreciative patient, to fits of choleric temper controllable only by large doses of sedatives.

Laboratory Data. (Bellevue Hospital, August 15, 1935.) Her blood pressure was 135/90 on both arms. Roentgen rays of the skull were normal. Six-foot heart plate revealed slight dilatation of the left ventricle. The encephalograms were of interest in that they revealed the typical unilateral "hydrocephalus *ex-vacuo*" characteristic of degeneration of one cerebral hemisphere. The red blood count was 4,900,000; hemoglobin, 90%; leukocytes, 7800 (normal differential count). N.P.N., 31; sugar, 87; calcium, 10.1; phosphorus, 4. Her spinal fluid contents were normal; initial pressure, 100.

Summary. 1. This record represents an 8-year follow-up of the neurologic and mental changes following ligation of the common carotid artery for pulsating exophthalmos (traumatic carotid-cavernous sinus aneurysm).

2. The encephalographic study illustrates the degree of brain damage which may follow ligation of the common carotid artery.

3. This case demonstrates the danger of completely ligating the common carotid artery without first encouraging the development of collateral circulation by digital compression.

I am indebted to Dr. Foster Kennedy, Director of the Neurological Service at Bellevue Hospital, for permission to report this case.

REFERENCES.

1. Dandy, W. E.: The Treatment of Carotid-cavernous Arteriovenous Aneurysms, Ann. Surg., **102**, 916, 1935.

2. deSchweinitz, G. E., and Holloway, T. B., quoted by deSchweinitz, G. E.: Diseases of the Eye, Philadelphia, W. B. Saunders Company, **9**, 640, 1921.

3. Fuchs, H. E.: Textbook of Ophthalmology, Philadelphia, J. B. Lippincott Company, **5**, 822, 1924.

4. Hallett, De W.: Pulsating Exophthalmos: Case Report, Am. J. Ophth., **11**, 710, 1928.

5. Hamby, W. B., and Gardner, J. W.: Treatment of Pulsating Exophthalmos, Arch. Surg., **27**, 676, 1933.

6. Homans, J.: Accidents and Precautions in Ligation of the Common Carotid Artery, Ann. Surg., **71**, 701, 1920.

7. Kolodny, A.: Pulsating Exophthalmos, Am. J. Ophth., **15**, 327, 1932.

8. Matas, R.: Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries, J. Am. Med. Assn., **63**, 1441, 1924.

9. Terry, D., and Mysel, P.: Pulsating Exophthalmos Due to Internal Carotid-Jugular Aneurysms, Ibid., **103**, 1036, 1934.

THE EFFECT OF THE INJECTION OF CERTAIN NITROGEN-CONTAINING COMPOUNDS INTO THE CISTERNA MAGNA ON THE BLOOD PRESSURE OF DOGS.

By Harry Resnik, Jr., M.D.,
ASSISTANT IN MEDICINE, VANDERBILT UNIVERSITY HOSPITAL,
AND
Morton F. Mason, Ph.D.,
INSTRUCTOR IN BIOCHEMISTRY AND RESEARCH ASSISTANT IN MEDICINE, VANDERBILT UNIVERSITY HOSPITAL, NASHVILLE, TENN.

(From the Departments of Medicine and Biochemistry, Vanderbilt University.)

At one time or another most of the urinary protein derivatives have been indicted as responsible for the uremic syndrome. The voluminous literature on this subject has been summarized by Fishberg,[1] who has pointed out that there is no convincing evidence to support the idea of the importance of any of these substances in the production of the increase in blood pressure, or of the other clinical phenomena which may accompany renal insufficiency. Attempts to produce in animals a syndrome resembling uremia by administering these compounds orally and intravenously have resulted in failure. However, we do not believe that such negative results can be regarded as conclusive, in view of the fact that we have recently observed in acute experiments, increase in blood pressure, muscular twitchings, and stertorous breathing following the intracisternal administration of certain electrolytes.[2] These effects were obtained from doses which were entirely ineffective when given intravenously. For these reasons it was decided to investigate the central action of the nitrogenous "retention" products by injecting them into the cisterna magna of dogs.

The effects of urea, uric acid, creatinin, ammonia, amino-acids and guanidin have been observed. The technique employed has been described in the previous communication.[2] The animals were anesthetized with sodium pentobarbital. The volume of fluid injected intracisternally was in each instance 1 cc.

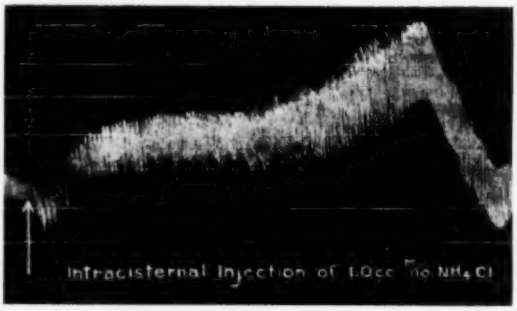
Results. *Urea.* The intracisternal injection of solutions of various strengths up to one-half molar did not cause significant change in blood pressure.

Sodium Urate. Saturated aqueous solutions containing approximately 6 millimols per liter (m. mols. p. L.) were ineffective. Inconstant effects were obtained with suspensions. In some instances suspensions containing 50 m. mols. p. L. were without effect; in other observations pronounced pressor responses occurred from the same dose.

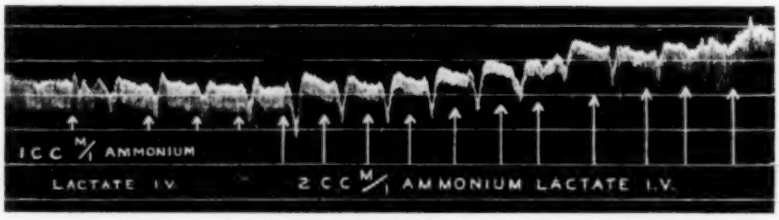
Creatinin. Solutions containing 250 and (500 m. mols. p. L.) were ineffective in 4 or 5 observations. The pressor response obtained in the fifth instance was apparently due to osmotic alterations as a rise in blood pressure was produced by the injection of equimolar amounts of sodium chlorid.

Ammonia. Constant results were not obtained from the intracisternal injection of ammonium chlorid. In the majority of instances this salt was without effect but in several animals pronounced and well sustained increase in blood pressure occurred (Fig. 1*a*). The cause of the variability of the response is unknown.

In several instances ammonium salts were given intravenously, the lactate being substituted for chlorid in order to avoid acidosis. Repeated injections of this salt caused temporary decline in blood pressure followed by a more sustained rise (Fig. 1*b*). However, pressor responses were not obtained until amounts approaching the lethal dose had been given.



A



B

FIG. 1.—The curve in this and other figures passes from left to right, and the distance between two adjacent horizontal lines indicates 20 mm. of mercury. The time curve in the lower portion of the record designates 6-second intervals. *A*. Intracisternal ammonium chlorid caused a marked rise in blood pressure. *B*. The effect of repeated intravenous injections of ammonium lactate is shown. Shortly after the last injection the animal died of respiratory paralysis.

Amino-acids. The concentrations employed of the several compounds varied according to their solubilities. Negative results were found with saturated solutions of cystin, cystein hydrochlorid, and tyrosin. Consistent pressor effects were not observed after intracisternal injections of d-arginin (100 m.mols p. L.), histidin dichlorid (50 m.mols p. L.), glycin (100 m.mols p. L.), leucin (100 m.mols p. L.), phenyl alanin (100 m.mols p. L.) or d-l alanin (50 m.mols p. L.). Striking rise in blood pressure occurred after injection of lysin picrate but the response could not be ascribed to the

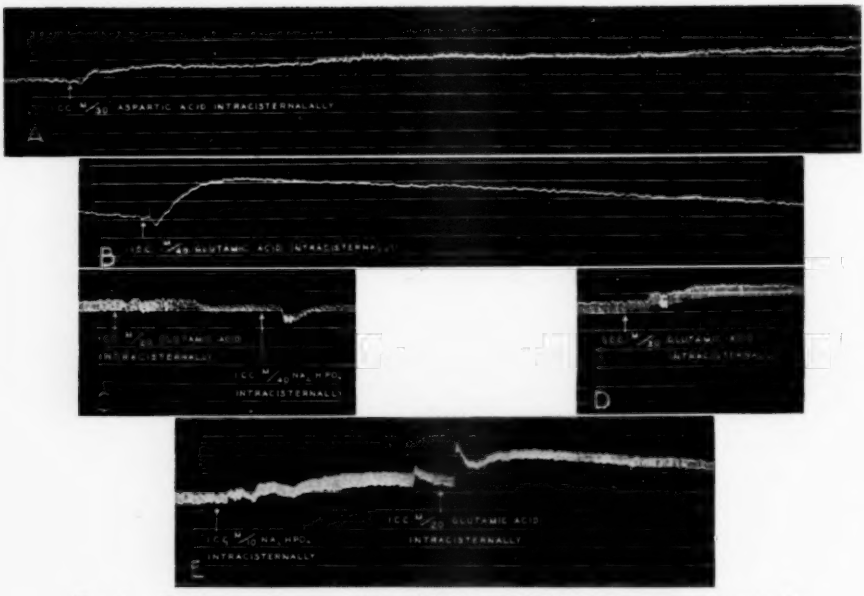


FIG. 2.—The two upper curves (*A* and *B*) illustrate the pressure responses to the intracisternal administration of aspartic acid and glutamic acid. The three lower curves were obtained from a different animal, which was at first unresponsive to glutamic acid (*C*). Following the intracisternal administration of phosphate the same amino acid caused a rise in blood pressure (*D* and *E*).

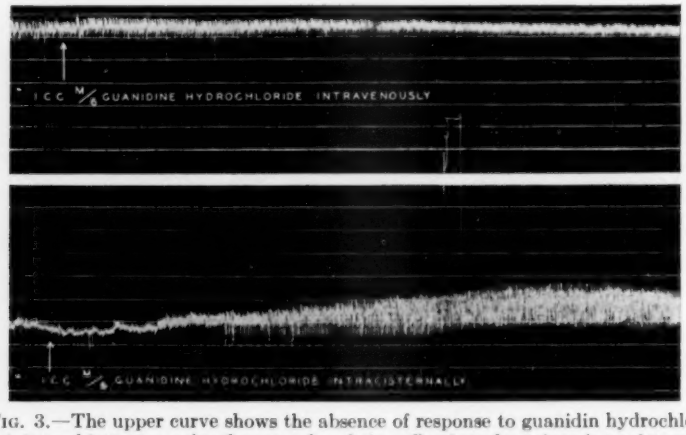


FIG. 3.—The upper curve shows the absence of response to guanidin hydrochlorid administered intravenously, the same dose being effective when given intracisternally as shown in the lower curve.

lysin for picric acid gave similar results. Aspartic acid (30 m.mols p. L.) and glutamic acid (50 m.mols p. L.) gave inconstant effects. When positive results were obtained with these two amino-acids the pressor responses usually lasted for 15 minutes or longer (Fig. 2) and were more persistent although less marked than those obtained

from some of the electrolytes investigated in our previous study.[2] It was found that the injection of calcium salts would lower the blood pressure which had been increased by glutamic acid. Diminution in the spinal fluid calcium by injecting di-sodium phosphate appeared to increase the pressor effect of glutamic acid (Figs. 2*c*, 2*d*, and 2*e*). However, calcium salts did not prevent the pressor response from a subsequent injection of glutamic acid.

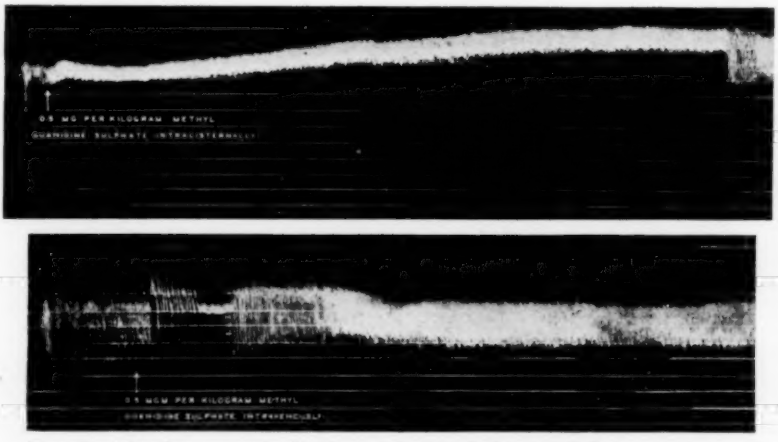


FIG. 4.—The time curve in the lower portion of the record designates 6-second intervals. Methyl guanidin sulphate intracisternally caused a slowly developing but sustained rise in blood pressure with an increase in respiratory fluctuation. The same dose was ineffective when later administered intravenously to the same animal.

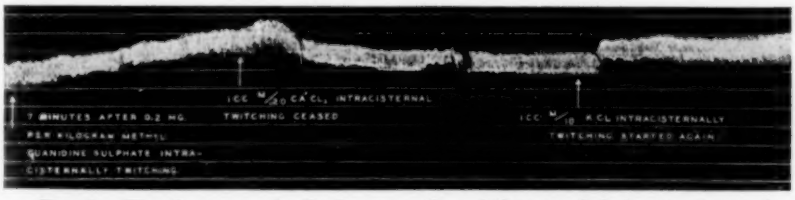


FIG. 5.—The time curve in the lower portion of the record designates 6-second intervals. At the onset of the record the blood pressure was rising and the animal had developed twitchings following the previous administration of methyl guanidin. Calcium chlorid caused a cessation of muscular twitchings and a fall in blood pressure, these effects being reversed by potassium chlorid. [Ordinarily, intracisternal injection of potassium salts is ineffective for several hours following the administration of calcium salts.[3] The record shows that the previous administration of guanidin interferes with the inhibitory action of calcium salts.]

Guanidin. Intracisternal injection of guanidin hydrochlorid caused rise in blood pressure when the same dose was ineffective intravenously (Fig. 3). Similar results were obtained with methyl guanidin sulphate (Fig. 4), which proved effective in smaller dosage than the guanidin itself. Intracisternal injections of as little as 0.2 mg. per kg. of methyl guanidin sulphate caused pronounced rise in blood pressure (Fig. 5).

The pressure effects of the guanidin compounds were slow in onset and often persisted for an hour or more. Marked respiratory stimulation and muscular twitchings usually accompanied the rise in blood pressure. Calcium salts administered intracisternally cotrolled the twtichings and diminished the blood pressure, regardless of whether the guanidin had been given intravenously or intracisternally (Figs. 5 and 6). Similar doses of calcium salts administered intravenously were less effective (Fig. 6).

The pressor effect of potassium chlorid when administered intracisternally can ordinarily be prevented by the previous injection of calcium salts.[2] However, when guanidin was given first the calcium was no longer effective in this respect (Fig. 5).

In a series of experiments Mason and Resnik[3] have shown that the lethal dose of calcium salts administered intracisternally to dogs

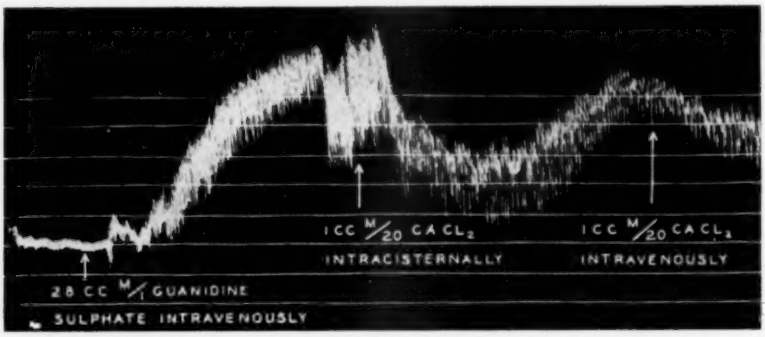


FIG. 6.—The time curve in the lower portion of the record designates 6-second intervals. Following a large intravenous dose of guanidin there was a marked increase in the blood pressure. Intracisternal administration of calcium chlorid produced a marked but temporary decline. The same dose of calcium chlorid administered intravenously had a less striking effect.

is in the general region of 0.3 to 0.4 mg. of calcium per kg. of body weight. In the present observations it was found that animals which had received guanidin either intravenously or intracisternally were able to tolerate larger doses of calcium chlorid.

Discussion. Of the several compounds investigated consistent and striking pressor effects were obtained only with guanidin and its methyl derivatives. Inconstant results were encountered with sodium urate, ammonia, aspartic acid and glutamic acid. As regards uric acid the positive results cannot be regarded as of significance because they were inconstant and were obtained only with suspensions, which may possibly have produced some mechanical irritation. Although ammonium salts caused pronounced rise in blood pressure in some experiments there is no reason to believe that they can be concerned in the elevation of blood pressure in patients with renal insufficiency, for the concentration of ammonia

in the body fluids never approaches the amounts necessary to cause increase in blood pressure in the animals. The same may be said of glutamic acid and aspartic acid although the possibility remains that under certain conditions the concentration of amino-acids in the cells of the nervous system may be greater than that in the body fluids.

It has been clearly shown by other investigators that guanidin has a peripheral pressor effect. [The literature on this subject has been summarized by Goldblatt and Karsner[4].] On the other hand, in our experiments the pressor effects of guanidin and of methyl guanidin were more pronounced when these substances were given intracisternally than when they were administered intravenously in equal dosage. Furthermore, the effects of guanidin were neutralized by the intracisternal administration of calcium salts in doses which were less effective intravenously. These observations indicate that under the conditions of our experiments the action of guanidin was chiefly central rather than peripheral.

The muscular twitchings, stertorous breathing and increase in blood pressure observed in the dogs which received guanidin constituted a symptom complex which was rather similar to that observed in many patients with advanced renal insufficiency. Whether or not this substance is concerned in the pathogenesis of the uremic symptom complex must be decided by future work. In such investigations the central as well as the peripheral action of guanidin must be taken into account.

Summary. The intracisternal injection of urea and creatinin did not increase the blood pressure. Uric acid (as sodium urate) and ammonia produced inconstant results. Of the several amino acids studied positive results were obtained only with aspartic acid and glutamic acid.

Guanidin hydrochlorid and methyl guanidin sulphate, when injected into the cisterna magna, caused striking and prolonged rise in blood pressure and muscular twitchings. Similar doses administered intravenously were less effective. Intracisternal injection of calcium salts diminished the blood pressure and controlled the muscular twitchings previously induced by guanidin. The observations indicate that guanidin has, in addition to the peripheral effect which has been described by others, a pronounced action on the central nervous system.

REFERENCES.

1. Fishberg, A. M. Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1931.

2. Resnik, H., Jr., Mason, M. F., Terry, R. T., Pilcher, C., and Harrison, T. R.: The Effect of Injecting Certain Electrolytes into the Cisterna Magna on the Blood Pressure, Am. J. Med. Sci., **191**, 835, 1936.

3. Mason, M. F., and Resnik, H. Jr.: The Toxicity of Calcium Salts when Administered into the Cisterna Magna of Dogs, J. Pharm. and Exp. Therap., **56**, 53, 1936.

4. Goldblatt, H., and Karsner, H. T.: Site of Pressor Action of Dimethylguanidin Sulphate, Ibid., **47**, 247, 1933.

BLOOD PHOSPHATASE AS AN AID IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE.

By Maurice M. Rothman, M.D.,
CHIEF OF THE GASTRO-ENTEROLOGICAL CLINIC, MT. SINAI HOSPITAL, MEDICAL SERVICE, NO. 2; INSTRUCTOR IN THE GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

David R. Meranze, M.D., B.S. Chem.,
PATHOLOGIST AND DIRECTOR OF LABORATORIES, MT. SINAI HOSPITAL,
AND

Theodore Meranze, M.D.,
ASSISTANT PATHOLOGIST, MT. SINAI HOSPITAL,
PHILADELPHIA, PA.

(From the Wards and Laboratories of the Mt. Sinai Hospital.)

Phosphatase is the term applied to one or more enzymes normally present in most tissues of the body and apparently concerned in the metabolism of bone. It is found in relatively large concentrations in bone, liver, kidney, and intestinal mucosa. It is also present in blood, bile and feces, and occasionally in traces in the urine.

Robison,[1] the first to demonstrate the presence of this enzyme in bone and ossifying cartilage, showed its intimate relationship to the process of bone formation. Since then it has been studied in the blood and its quantitative estimation in blood serum and plasma has been of considerable diagnostic value in a limited group of pathologic conditions, particularly diseases of bone.[2–5] The serum and plasma phosphatase have been reported to be moderately increased in cases of pronounced local bone atrophy, generalized osteoporosis and osteomalacia. In the few reported cases of hyperparathyroidism the findings are 4 and 5 times the normal. Active infantile rickets are found to be associated with very high phosphatase readings, reaching on occasions values from 10 to 13 times the normal figures. The greatest elevations have been found in florid polyostotic Paget's disease, in which condition values as high as 30 times the normal have been reported. In osteogenic sarcoma, metastases to bone and fragilitas ossium the phosphatase value is said to be moderately increased. Physiologically, the phosphatase content of the blood plasma is slightly increased after the ingestion of carbohydrates.[6]

Roberts,[7] who was among the first systematically to study the blood phosphatase in disease states, observed high values in the 3 cases of jaundice which he had included in his series. He noted, moreover, a striking difference in the phosphatase content of the plasma of the 2 cases of obstructive and the 1 case of non-obstructive jaundice studied. This observation led him, in a subsequent work,[8] to study the phosphatase values in a series of 52 cases of jaundice, 21 of which were obstructive, 31 non-obstructive. He concluded that by means of the phosphatase level of the blood, "toxic, infectious and catarrhal jaundice may be readily distinguished from jaundice of the obstructive type." In this series he found, as others

have also, normal phosphatase values in 5 cases of hemolytic jaundice. Subsequent workers, Bodansky and Jaffe,[9] Armstrong, King and Harris,[10] Greene, Shattuck and Kaplowitz,[11] also observed a rise of phosphatase value in all cases of jaundice other than that of hemolytic origin. Bodansky and Jaffe[12] ligated the common bile duct of a dog and noted the progressive elevation in the serum phosphatase paralleling the rise in the serum bilirubin. They believed, however, that the determination of plasma phosphatase was of no value in differentiating between obstructive and non-obstructive jaundice.

Armstrong, King and Harris[10] confirmed these ligation experiments in 19 dogs and, after releasing the obstruction in 2 animals, noted a return to normal in the phosphatase and bilirubin values. In 1 the drop in the plasma phosphatase was immediate, in the other the return to a normal phosphatase value was more gradual. They believed that this slow return to normal was the result of damage to the liver cells incurred during the period of biliary obstruction. They also report phosphatase studies in 5 clinical cases of obstructive jaundice, obtaining results comparable to those in the experimental animals whose common bile ducts were ligated. Armstrong and King[13] later produced a toxic hepatitis in 8 dogs (chloroform, phosphorus and toluylendiamin) with a resulting elevation in the phosphatase values. In 2 other dogs a marked phenylhydrazin hemolysis, in accord with results of other workers, produced no elevation of phosphatase. The elevation of phosphatase which developed in the 8 animals with toxic hepatitis, however, at no time reached the levels obtained in the cases of experimental obstructive jaundice, even in the instances of the most severe liver damage. They concluded from these experimental studies that the test may, with further investigation, become useful in the differential diagnosis of jaundice. Greene, Shattuck and Kaplowitz,[11] on the other hand, concluded from a series of clinical cases that the test was of no value in differentiating between obstructive and non-obstructive jaundice.

It is the purpose of this paper to present clinical data which we believe substantiate Roberts' original assertion concerning the clinical usefulness of phosphatase determinations in the differential diagnosis of jaundice.

It is unnecessary to point out the importance of determining the mechanism of the production of jaundice in particular cases, and the desirability of arriving at some notion of the pathologic state of the liver under such conditions. Soffer,[14] in a recent review of liver function tests, has again emphasized the profound inadequacies in the present state of our knowledge. Though nearly all the liver function tests suggested at various times have contributed information of value and, in some instances, have been of aid in differential diagnosis, it is generally agreed, by most authorities, that individually and collectively they fall far short of our needs. We feel that the addition of the results of the phosphatase test contributes information of definite value.

The classification of jaundice under which we have arranged our cases is the following orthodox grouping into:

1. Obstructive jaundice, *i. e.*, jaundice due to extrahepatic obstruction including cases of obstruction due to stones in the common bile duct, neoplasm, etc.

2. Hepato-cellular or non-obstructive jaundice, *i. e.*, jaundice resulting from direct injury to the parenchymal liver cell, or to cholangitis, such as is the case in so-called "acute catarrhal jaundice."

3. Hemolytic jaundice.

Methods. At present several methods are used to determine the phosphatase activity of the blood.[7,15,16,17] They are essentially similar in principle. They consist in measuring the phosphorus set free as inorganic phosphate when the enzyme present in the blood is allowed to act on a phosphoric acid ester substrate under standardized conditions. Some methods employ blood serum, others plasma; each varies in the nature of the buffer, and time of incubation, and some in the methods employed in determining the inorganic phosphorus content of the blood. Unfortunately there is at present no general agreement among workers in reporting the results of phosphatase determinations. The units of measurement in the various methods vary. We have employed a slight modification of Roberts'[7] method in our present study which is practical, simple, time saving and entirely satisfactory for clinical purposes. The method is as follows: The determinations are made on fasting blood. Two cc. of plasma (citrated blood) is mixed with 2.3 cc. of distilled water and 0.7 cc. of N/10 sodium hydroxid. This produces a pH of approximately 8.9. To this is added 1 cc. of a 1% solution of sodium beta-glycerophosphate. The mixture is then incubated at 37.5° C. for 2 hours, after which its inorganic phosphorus content is determined by the method of Fiske and Subbarow. At the same time the initial inorganic phosphorus content of the plasma is determined using another 2 cc. of the original blood. Both of these values are determined in mgm. per 100 cc. of blood plasma. The difference between these two values represents the number of mgm. of inorganic phosphorus liberated by the enzyme, phosphatase, from the substrate under the above conditions. Each mgm. thus obtained is expressed as units of phosphatase per 100 cc. of blood plasma.

In addition to the determination of the phosphatase in cases of jaundice, during the past 3 years, we have also studied the values on a series of cases exhibiting no jaundice and without, as far as we were able to determine, any appreciable liver damage, or any of the other pathologic states known to influence phosphatase values. These include 18 cases of cholecystitis with and without stones. Table 1 lists the values in these cases.

TABLE 1.—PHOSPHATASE VALUES IN CASES WITHOUT JAUNDICE OR LIVER DISEASE.

No. of cases.	Age range, years.	Units of phosphatase.
10	1 to 15	3.20 to 10.80
5	16 to 20	1.70 to 5.80
14	21 to 30	2.00 to 6.00
19	31 to 40	1.00 to 5.90
9	41 to 50	2.30 to 4.40
10	51 to 60	1.60 to 6.00
5	61 to 70	2.30 to 4.90
2	71 to 80	1.80 to 3.00

Taking into consideration the results listed in Table 1 and those given by Roberts,[7] we have regarded as normal for adults, phosphatase values less than 6 units, and for children values less than 15 units.

TABLE 2.—CASES OF OBSTRUCTIVE JAUNDICE.

No.	Name.	Age.	Date.	Units of phosphatase.	Serum bilirubin, mgm.	Remarks and diagnoses.
1	R. G.	20	9/14	20.48	5.28	Galactose excretion in 5 hours
			9/17	22.02	4.28	was 2.9 gm.
			9/18	11.08	2.47	Operation 9/20—stone in com-
			9/18	12.64	3.92	mon duct.
			9/20	14.98	5.78	Expired 9/23. No necropsy.
2	S. H.	52	1/22	23.40	5.09	Roentgen ray showed gall
			1/27	15.54	Not done	stones.
3	L. M.	19	12/28	20.58	2.12	Operation on 1/26 revealed
			1/2	19.50	0.50	gall stones.
			1/11	14.04	0.78	
			1/30	6.70	0.54	
4	S. R.	60	12/26	18.82	5.42	Diabetes mellitus. Operation
			1/2	18.06	6.23	on 1/4—stone removed; gall
			1/11	5.40	5.08	bladder gangrenous. Eleva-
			1/16	9.22	3.08	vation of phosphatase on
			1/19	23.92	4.06	1/19 suggests partial ob-
			1/25	15.08	3.90	struction. Patient drained
			2/1	24.42	1.48	bile until discharge.
			2/13	23.18	1.42	
			2/20	20.08	1.32	
5	A. O.	65	11/11	19.04	1.56	Roentgen ray showed gall stones.
6	L. S.	65	12/7	10.18	1.24	On 11/28, icterus index 72. On
	Readmission		2/24	1.36	8.25	11/29 stones found in com-
			2/26	7.00	11.31	mon bile duct. Readmitted. Expired on 3/1. Necropsy: sub-diaphragmatic abscess and acute hepatitis.
7	H. S.	52	6/7	19.00	0.75	Biliary drainage revealed crys-
			6/8	15.40	0.45	tals and pigment. Diagno-
			6/13	10.30	0.37	sis of gall stones.
8	J. D.	53	7/13	21.48	1.55	
			7/18	17.26	1.53	
9	R. P.	70	4/12	18.32	2.58	Operation on 4/12, and stones
			4/16	13.12	0.96	were found in the common
			4/21	7.00	0.31	bile duct.
10	J. H.	35	3/15	14.14	0.62	Biliary drainage showed cal-
			3/17	14.30	0.58	cium bilirubinate pigment
			3/19	17.98	1.65	and cholesterin crystals.
			3/21	11.18	Not done	Operation on 3/22: showed
			3/24	6.92	0.86	gall stones.
11	S. F.	60	6/12	12.24	2.26	Operation on 6/13: common bile duct filled with stones.
12	G. Y.	52	11/9	11.36	0.58	Biliary drainage; pigment and crystals.
13	A. K.	46	7/30	7.46	0.90	Operation, 7/31: gall stones.
			8/2	6.10	0.81	
			8/8	4.18	0.35	
14	B. W.	42	2/1	10.56	1.85	Operation, 2/15: gall stones
			2/6	13.04	0.52	and a dilated common bile
			2/20	10.58	0.92	duct.
15	J. B.	40	11/17	14.44	9.24	Block in sphincter of Oddi by plug of mucus and duodenitis.

TABLE 2.—CASES OF OBSTRUCTIVE JAUNDICE—*Continued.*

No.	Name.	Age.	Date.	Units of phosphatase.	Serum bilirubin, mgm.	Remarks and diagnoses.
16	J. P.	60	8/22	20.96	1.81	On 2/13, 6 months before present admission, had gall bladder operation, now postoperative adhesions.
			8/25	17.66	2.00	
17	T. W.	53	11/2	12.44	7.29	Two previous operations. Now periductal adhesions.
18	C. H.	26	12/19	3.00	1.01	Operation, 1/9: stone in the cystic duct.
			12/21	4.50	0.58	
			12/28	4.62	0.70	
			1/6	2.94	0.45	
19	M. M.	46	3/23	20.76	Not done	Icterus index on these successive dates were 16; 22.4; 47.6; 14.8; 6.2 and 5.1. The serology was positive. Operation, 4/5: dilated common bile duct due to stones.
			3/27	19.32	"	
			3/30	21.40	"	
			4/3	19.80	"	
			4/12	21.64	"	
			4/19	12.70	"	
20	N. W.	38	12/19	6.04	1.42	Operation, 12/23: gall stones and acute pancreatitis.
			12/22	6.80	1.65	
			1/11	4.86	0.46	
21	S. M.	31	5/29	10.80	1.09	Gall stones with chronic hypertrophic biliary cirrhosis. Urobilinogen were 1 to 200 and 1 to 400.
			5/31	13.18	0.74	
			6/2	13.78	1.35	
			6/5	5.22	0.42	
22	F. P.	27	3/8	8.18	3.99	Biliary drainage showed pigment and crystals.
			3/10	7.44	3.90	
			3/13	4.84	1.52	Operation, 3/22: gall stones with adhesions.
			3/19	3.84	0.64	
			3/21	3.48	Not done	
23	D. W.	57	1/13	22.68	1.08	Necropsy, 2/15: carcinoma of head of pancreas with metastases to liver.
			1/20	20.78	3.11	
			2/8	14.56	2.63	
			2/12	20.30	Not done	
24	A. K.	70	11/11	10.50	7.34	Necropsy, 11/24: carcinoma of head of pancreas. Galactose excretion in 5 hours was 3 gm.
			11/23	11.00	9.23	
25	S. B.	65	4/24	25.04	9.50	Necropsy, 5/15: carcinoma of head of pancreas.
			4/26	25.56	8.97	
			4/28	21.80	10.58	Galactose excretion in 5 hours was 3 gm.
			5/2	24.64	9.79	
			5/5	20.16	7.84	
			5/8	23.72	7.44	
26	S. W.	62	5/5	23.90	6.48	Cholecystostomy, 5/12.
			5/10	24.78	7.98	
			5/16	11.94	4.74	Necropsy, 5/28: carcinoma of head of pancreas.
			5/19	Not done	4.76	
27	M. C.	60	9/14	21.60	8.70	Necropsy, 9/26: carcinoma of head of pancreas with liver metastases.
			9/17	22.08	7.56	
			9/20	19.58	12.62	
			9/22	21.62	12.91	
28	S. F.	70	7/26	20.20	6.67	Necropsy, 8/4: carcinoma of head of pancreas.
			8/4	17.56	6.60	
29	Y. G.	62	10/11	19.04	16.56	Diabetes mellitus with carcinoma of head of pancreas.
			10/21	10.60	10.89	
			12/21	18.60	16.23	

Our series consists of 53 cases of jaundice of various mechanisms, and are listed in Tables 2 and 3. The phosphatase determinations were repeated at frequent intervals in many instances. Quantita-

tive serum bilirubin determinations were done simultaneously in most instances. Only those cases in which the diagnosis was well established by clinical and laboratory findings were included in this study.

In Table 2 are listed the results of a series of 29 cases of obstructive jaundice. Several etiologic factors were involved as can be seen from this table. The generally high phosphatase values are striking. In all but 4 of the 29 cases the phosphatase values were greater than 10 units. These findings are in marked contrast with those obtained in the series of non-obstructive cases listed in Table 3. In Case 1, the medical and surgical consultants disagreed as to the diagnosis, the latter inclining to a diagnosis of toxic hepatitis refused to operate. On September 20, following a severe chill, the patient was operated upon and a stone was found impacted in the common bile duct. In Case 6, the phosphatase reading of 10.18 units was obtained during the period of convalescence, following a cholecystectomy for common duct obstruction. When the patient was readmitted a medical diagnosis of recurring common duct obstruction was made. The phosphatase values obtained at this time, 1.36 and 7.00 units, suggested rather a jaundice resulting from a non-obstructive mechanism. An acute hepatitis was found at necropsy.

In Table 3 are listed the findings in 24 cases of non-obstructive jaundice. In 18 of these the phosphatase values lie at or below 10 units. In 4 cases (Nos. 33, 39, 41 and 43) values slightly greater than 10 units were obtained. In the remaining 2 cases (Nos. 34 and 47) values as high as 17.26 and 11.68 units were obtained respectively. These last 2 were children in whom phosphatase values as high as 15 units are considered normal. It is therefore justifiable to regard the results obtained in Case 34 as moderately increased above normal, and that in Case 47 as falling within the normal range. It is because of these findings and those listed in Table 2 that we have come to agree with Roberts in his assertion that in cases of jaundice, phosphatase values up to 10 units indicate that the jaundice is non-obstructive in etiology, and values above 10 units indicate an obstructive mechanism.

Discussion. In commenting on the results in Table 3, we have called attention to a number of instances in which the phosphatase values were greater than 10 units. We cannot, however, entirely agree with Roberts[8] when he states that it is not necessary to know the concomitant serum bilirubin values in order to interpret the phosphatase readings. We believe that a comparison of the relative increase in the values of phosphatase and serum bilirubin above their respective normals gives additional aid in diagnosis, and in particular makes possible a correct interpretation of those borderline values of 10 units or slightly above. The basis for this belief lies in the observation that in obstructive jaundice the rise in the phosphatase and serum bilirubin tends to run parallel until the limits of the phosphatase values are reached. In non-obstructive

TABLE 3.—CASES OF NON-OBSTRUCTIVE JAUNDICE.

No.	Name.	Age.	Date.	Units of phosphatase.	Serum bilirubin, mgm.	Diagnosis.	Remarks.
30	A. R.	30	6/13	6.30	8.90	Hepato-cellular jaundice	Urobilinogen 1:100. Galactose excretion 4 gm. in 5 hours.
			6/18	7.30	4.60		
31	F. V.	17	6/9	10.00	10.00	Hepato-cellular jaundice	Urobilinogen 1:100. Galactose excretion 4.7 gm. in 5 hours.
			6/13	5.50	6.00		
			6/18	8.00	5.00		
32	R. D.	24	3/16	5.84	2.30	Gall stones, hepatitis, cystic duct obstruction	Urobilinogen 1:100. Galactose excretion 2 and 4.78 gm. in 5 hours. Positive serology. Operation.
33	B. S.	37	5/25	10.50	12.18	Hepato-cellular jaundice	Urobilinogen 1:50. Galactose excretion 1.35, 3.08 and 5.55 gm. in 5 hours. Chronic alcoholic. Takata-Ara test positive.
			5/28	7.92	8.19		
			6/9	9.00	2.40		
			6/13	9.00	1.84		
34	N. W.	11	1/25	10.12	2.41	Hepato-cellular jaundice	Urobilinogen 1:40. Roentgen ray normal gall bladder, no stones.
			2/2	17.26	1.25		
			2/6	16.20	0.54		
35	W. H.	35	1/20	3.14	3.00	Hepato-cellular jaundice	Urobilinogen 1:20. Galactose excretion 0 gm. in 5 hours. Roentgen ray no gall stones.
			1/22	4.34	3.39		
			1/23	2.86	1.89		
36	C. F.	36	2/14	9.28	8.64	Hepato-cellular jaundice	Urobilinogen 1:80. Galactose excretion 0 gm. in 5 hours.
			2/21	8.68	4.71		
37	J. J.	38	8/17	8.04	5.00	Hepato-cellular jaundice	Urobilinogen 1:50. Galactose excretion 6.7 gm. in 5 hours.
38	R. C.	25	12/3	6.34	7.10	Hepato-cellular jaundice	Urobilinogen 1:20.
39	S. S.	26	1/9	11.38	12.40	Hepato-cellular jaundice	Urobilinogen 1:8. Galactose excretion 2.2 gm. in 5 hours.
			1/19	7.24	5.90		
40	A. I.	28	12/18	9.38	7.10	Hepato-cellular jaundice	Galactose excretion in 5 hours 0.83 gm.
41	T. P.	21	12/29	10.34	9.76	Hepato-cellular jaundice	Urobilinogen 1:20. Galactose excretion 4.79 gm. in 5 hours.
			1/2	9.02	5.79		
			1/21	3.78	0.72		
42	E. K.	7	11/10	9.52	7.76	Hepato-cellular jaundice	Urobilinogen 1:20.
			11/12	10.04	6.67		
			11/20	9.04	5.78		
			12/5	7.04	2.20		
43	N. K.	50	5/8	9.84	14.30	Acute yellow atrophy	Galactose tolerance test unsatisfactory.
			5/12	10.70	17.80		
44	J. P.	53	2/11	5.84	0.84	See Case 16	Admission prior to operation for cholecystitis.
45	D. G.	24	5/16	6.66	5.95	Hepato-cellular jaundice	Urobilinogen 1:100.
			5/19	8.40	6.92		
			5/23	4.16	1.20		
			5/28	1.56	0.99		
			6/8	3.94	0.21		
46	S. G.	6	3/1	8.82	3.77	Hepato-cellular jaundice	Urobilinogen 1:20.
			3/10	8.98	1.94		
			3/21	4.46	0.67		
47	E. K.	12	5/15	11.68	0.87	Hepato-cellular jaundice	Urobilinogen 1:20.
48	H. B.	43	7/21	4.55	0.70	Luetic hepatitis	Urobilinogen 1:90. Serology positive.
49	N. L.	53	11/25	2.58	3.43	Luetic hepatitis	Serology positive.
50	H. A.	63	1/25	1.92	1.54	Toxic hepatitis	Diabetes mellitus.
			2/1	3.00	0.60		
51	J. R.	66	7/13	4.32	0.76	Toxic hepatitis	Uremia.
52	D. W.	40	12/7	3.92	1.12	Pernicious anemia	
			12/14	3.22	0.75		
53	G. T.	48	5/25	8.32	1.64	Portal cirrhosis	Urobilinogen 1:100. Galactose excretion 1.36 gm. in 5 hours.

cases, on the other hand, in spite of the progressive increase in serum bilirubin the phosphatase values rarely rise above 10 units and no parallelism was noted. This is illustrated in the group of Cases 39, 40 and 41. Here we found phosphatase values ranging from 9.38 to 11.38 units, with serum bilirubin values of from 7.10 to 12.40 mgm. It is in such borderline cases that were the phosphatase alone considered it would be difficult to arrive at a definite interpretation. We would be forced, if we adhered too strictly to the value of 10 units, as the dividing line, to consider one of these (Case 39) as an instance of obstructive jaundice. In conjunction with the serum bilirubin estimation, however, the interpretation becomes clearer. The high phosphatase values usually associated with elevated bilirubin values in obstructive jaundice is absent. It would therefore seem justifiable to assert that the phosphatase values slightly greater than 10 units, if associated with a markedly elevated bilirubin justify the presumptive diagnosis of a predominantly non-obstructive mechanism. In the light of this qualification there need be in most instances no difficulty in the interpretation of borderline values.

We believe, therefore, from the striking differences in phosphatase values obtained in the two great groups of cases of jaundice discussed, that the blood phosphatase reflects two mechanisms, that due to obstruction and that due to a more direct involvement of the liver parenchyma. When both of these disturbances are present the extent of each can be roughly gauged by comparing the bilirubin with the phosphatase values. The phosphatase findings should, we feel, be considered as representing a composite of effects the dominant pathologic state exerting the greater influence on its value.

It is of course apparent from our data that the test can serve only as a means of differentiating between the two classes of jaundice we have listed, in the absence of other conditions affecting phosphatase. The specific etiology must, at the present time, be inferred from other studies. In its ability to help differentiate between an obstructive and an non-obstructive jaundice, however, the phosphatase determination appears to be superior to other available tests, and in particular, the galactose tolerance test, when the latter is used to detect acute parenchymal liver disease. Thus, the phosphatase findings were correct in most of the adult cases of non-obstructive jaundice, while in a considerable number of instances the galactose tolerance test was in error (Table 3). Only after repetition of the galactose tolerance test was the excretion, in some instances, elevated to levels diagnostic of hepato-cellular jaundice.

In our work we now regard the phosphatase values as a sensitive indicator of liver dysfunction in obstructive jaundice. In Case 7, the phosphatase value remained elevated long after the serum bilirubin and other findings had returned to normal. In this respect it appears comparable to the urobilinogen determinations in case of non-obstructive jaundice. One of us (M. M. R.)[18] has shown

that urine urobilinogen will frequently remain increased in cases of hepato-cellular jaundice long after other tests have reached normal levels. It is also apparent from our studies that in some instances too much reliance must not be placed upon a single phosphatase determination. If, for example, a first estimation of phosphatase were to be made early in the onset of obstructive jaundice, as the jaundice is developing, it is conceivable that the phosphatase value, rising slowly in proportion, may not as yet have reached diagnostic heights. The low phosphatase value obtained under such conditions may be misleading. It is therefore necessary in some instances where the clinical impression of obstructive jaundice seems well founded, and the serum bilirubin only slightly elevated, to repeat both determinations within a few days in order to determine the progress of the disease. A similar caution must be exercised in the converse state. Furthermore, if the patient has had present a ball-valve stone or a biliary colic, due to the passage of stone too small to have produced more than a fleeting or latent jaundice, the phosphatase and serum bilirubin values may be only slightly increased. We have also noted a tendency, in insulin-treated diabetics with jaundice, for the phosphatase values to remain high postoperatively for a longer period of time than usual.

Summary. 1. The blood phosphatase values have been studied in a large series of clinical cases of jaundice, both obstructive and non-obstructive.

2. The phosphatase values in most of the cases of obstructive jaundice were found to have values greater than 10 units, while in the non-obstructive cases the values were found to be 10 units or less.

3. We, in agreement with Roberts, have therefore chosen a phosphatase value of 10 units to be the dividing line between cases of obstructive and non-obstructive jaundice. Certain considerations are listed which make more readily interpretable borderline cases.

4. The phosphatase determination has proven, in our studies, to be of greater value than any other available test in differentiating between obstructive and non-obstructive jaundice.

REFERENCES.

1. Robison, R.: Possible Significance of Hexosephosphoric Esters in Ossification, Biochem. J., **17**, 286, 1923.

2. Kay, H. D.: Phosphatase in Growth and Disease of Bone, Physiol. Rev., **12**, 384, 1932.

3. Kay, H. D.: Plasma Phosphatase. (2) The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem., **89**, 249, 1930.

4. Smith, J.: Plasma Phosphatase in Rickets and Other Disorders of Growth, Arch. Dis. Child., **8**, 215, 1933.

5. Bodansky, A., and Jaffe, H. L.: Serum Phosphatase in Diseases of the Bone: Interpretation and Significance, Arch. Int. Med., **54**, 88, 1934.

6. Bodansky, A.: Non-osseous Origin of Serum Phosphatase: Its Increase After Ingestion of Carbohydrates, J. Biol. Chem., **104**, 473, 1934.

7. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exp. Path., **11**, 90, 1930.

8. Roberts, W. M.: Blood Phosphatase and the Van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. Med. J., **1**, 734, 1933.
9. Bodansky, A., and Jaffe, H. L.: Serum Phosphatase of Non-osseous Origin: Significance of the Variations of Serum Phosphatase in Jaundice, Proc. Soc. Exp. Biol. and Med., **31**, 107, 1933.
10. Armstrong, A. R., King, E. J., and Harris, R. I.: Phosphatase in Obstructive Jaundice, Canadian Med. Assn. J., **31**, 14, 1934.
11. Greene, C. H., Shattuck, H. F., and Kaplowitz, L.: The Phosphatase Content of the Blood Serum in Jaundice, J. Clin. Invest., **13**, 1079, 1934.
12. Bodansky, A., and Jaffe, H. L.: Increase of Serum Phosphatase After Bile Duct Ligation in Dog, Proc. Soc. Exp. Biol. and Med., **31**, 1179, 1934.
13. Armstrong, A. R., and King, E. J.: Serum Phosphatase in Toxic and Hemolytic Jaundice, Canadian Med. Assn. J., **32**, 379, 1935.
14. Soffer, L. J.: Present Day Status of Liver Function Tests, Medicine, **14**, 185, 1935.
15. King, E. J., and Armstrong, A. R.: A Convenient Method for Determining Serum and Bile Phosphatase Activity, Canadian Med. Assn. J., **31**, 376, 1934.
16. Jenner, H. D., and Kay, H. D.: A Clinical Method for the Determination of the Plasma Phosphatase, Brit. J. Exp. Path., **13**, 22, 1932.
17. Bodansky, A.: Determination of Serum Phosphatase: Factors Influencing the Accuracy of the Determination, J. Biol. Chem., **101**, 93, 1933.
18. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, J. Am. Med. Assn., **91**, 1768, 1928.

We wish to thank Dr. H. L. Bockus, Professor of Gastro-enterology, Graduate School of Medicine, University of Pennsylvania, for permitting us the use of cases from his wards.

We wish also to express appreciation to Mr. B. Ross for his technical assistance in this work.

COMPARATIVE ADVANTAGES AND FURTHER MODIFICATION OF THE BILIRUBIN EXCRETION TEST FOR HEPATIC FUNCTION.

By Louis J. Soffer, M.D.,

INSTRUCTOR IN MEDICINE, THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL,

AND

Moses Paulson, B.S., M.D., F.A.C.P.,

ASSOCIATE-IN-MEDICINE, PHYSICIAN (GASTRO-ENTEROLOGIST) TO THE DIAGNOSTIC CLINIC, AND ASSISTANT VISITING PHYSICIAN, THE JOHNS HOPKINS HOSPITAL AND UNIVERSITY, BALTIMORE, MD.

(From the Chemical and Gastro-enterologic Divisions of the Department of Medicine.)

The measurement of the excretion of intravenously injected bilirubin as a means of determining the existence of hepatic dysfunction was originally devised by Eilbot,[1] and was introduced into this country by Harrop and Barron.[2] The procedure, with the modifications to be described, appears to be the most delicate excretory test of liver function. It is hoped that the following data, and the improvements in the procedure resulting in the simplification of the test, will encourage its more widespread use.

The use of the bilirubin excretion test is limited to those patients who show no elevation of circulating blood bilirubin beyond 1 mg. %. In the presence of hyperbilirubinemia, the retention of injected bilirubin has no significance, since, obviously, the liver cannot adequately handle the amount of bile pigment in the blood prior to performance of the test.

In investigating the comparative merits of this method with bromsulphalein, levulose tolerance, galactose tolerance, urobilinogen and Van den Bergh procedures, it was found that the bilirubin excretion test yielded the greatest incidence of positive results.[3] However, for closer evaluation, a comparison was made between bilirubin and bromsulphalein, both excretory gauges of hepatic function.

We have had no experience with rose bengal which is also used to determine the excretory capacity of the liver. We were influenced by Greene's observation[4] that in a study of more than 700 cases "there is very little difference in the significance of the various dyes. Phenoltetrachlorphthalein, bromsulphalein and rose bengal all show essentially the same type of changes." Therefore, the bromsulphalein test has been used because it is the simplest to perform.

The relative merits of bromsulphalein and bilirubin are demonstrated in Table 1. In 18 cases in which there was clinically well-defined, although slight, liver damage, the bilirubin test was positive in 16, while in only 3 instances was functional derangement manifested by the bromsulphalein test. In 15 cases in which there were no clinical data to indicate hepatic involvement but where such a possibility was suspected (see Miscellaneous in Table 1), 17 com-

Table 1.—Comparative Value of Bilirubin and Bromsulphalein Liver Function Tests.

Type of hepatic damage.	No. of cases.	Comparative tests.	No. of positive results.	
			Bilirubin tests.	Bromsulphthalein tests.*
Cirrhosis of liver without ascites	12	12	11	2
Malignancy of the liver—2°	3	3	2	0
Diffuse liver damage with jaundice directly after jaundice had subsided	3	3	3	1
Miscellaneous group: no clinical data suggesting liver damage, but reason to suspect it	15†	17	12	3
Total	33	35	28	6

* 5 mg. per kilo.

† Three of these cases, all of which were among the negatives, received 2 mg. bromsulphalein per kilo.

parative studies yielded 12 positive bilirubin and 3 positive bromsulphalein tests. In no instance was the bilirubin test negative when the bromsulphalein was positive. This becomes doubly significant in the face of the fact that in 30 of the 33 cases the dose of bromsulphalein intravenously administered was 5 mg. per kilogram —$2\frac{1}{2}$ times the amount originally advocated by its sponsors, Rosenthal and White.[5] In 3 cases (in the Miscellaneous group), the 2-mg. dose was used. Retentions of bromsulphalein in excess of 10% at the end of $\frac{1}{2}$ hour, as originally postulated with the 2-mg.

dose, were regarded as abnormal irrespective of the amount employed. Retentions of bilirubin in excess of 5% at the end of 4 hours were regarded as abnormal. Thus in a total of 33 cases in which 35 comparative tests had been made, 28 showed abnormal retention of injected bilirubin and 6 showed abnormal retention of injected bromsulphalein. It should again be emphasized that the bilirubin test is frequently positive in mild instances of liver damage. Hence the bilirubin excretion test is of value where the other tests usually yielded negative results.

The reasons for the increased sensitivity of this test are probably dependent on the following factors: (1) The excretory function of the liver is being measured by its ability to handle a substance which is normally manufactured by the body and normally excreted by the liver. (2) In a good many instances the excretory function of the liver is the first to be disturbed. Hence, the use of a physiological substance such as bilirubin seems to be the most sensitive index for appraisal. (3) The usual excretory tests for hepatic function are based on the selective activity of the liver to remove foreign products, as dyes, from the circulating blood stream and excrete them into the duodenum. However, this would appear to be only partly true, since there is some evidence to indicate that a dye such as bromsulphalein, when injected into the blood stream, is not removed by the liver in its entirety. At least a portion of it is phagocytosed by the reticulo-endothelial cells.[6] On the other hand, injected bilirubin circulates freely and is excreted *in toto* by the liver, except in obstructive jaundice. In this condition, according to Kanner,[7] the storage of bile pigment takes place in the reticulo-endothelial cells. Yet this is of no practical moment, since the bilirubin hepatic excretion test is not employed in the presence of a serum bilirubinemia in excess of 1 mg. %.

It is not to be inferred that the bilirubin excretion test is to be used to the exclusion of all other laboratory methods in determining hepatic activity. Even though we believe it to be the best single procedure, the apparent inadequacy of liver function tests is partly due to efforts to make one method a gauge for all of the manifold liver tasks. Much information of diagnostic and prognostic significance can be derived from the frequent use of a variety of procedures, due consideration being given to their indications and limitations.[3]

The method originally devised by Eilbot for the performance of the bilirubin liver function test is rather difficult and time-consuming. We have introduced certain modifications which have been previously described.[8,9] In order to further simplify the performance of the test, we have constructed a series of standards which may be used in place of the colorimeter. The essential advantages of the standards are simplicity of performance and reduction of costs. The use of the colorimeter requires a certain amount of diligent

application and experience which may not be available to many physicians desiring to employ this test. The clinical results obtained with the standards compare quite accurately with those of the colorimeter (Table 2) and such differences as are noted are of no significance in interpreting the results.

TABLE 2.—COMPARATIVE COLORIMETER AND STANDARDS. BILIRUBIN RETENTION DETERMINATIONS.

Case.	Colorimeter, %	Standards, %	Difference, %
1	14.2	18.0	3.8
2	28.5	32.8	4.3
3	17.5	19.2	1.7
4	4.0	4.0	0
5	24.1	24.0	0.1
6	11.5	15.3	3.8
7	25.1	28.2	3.1
8	18.2	18.4	0.2
9	47.1	54.0	6.9
10	17.8	13.1	4.7
11	7.0	8.0	1.0
12	13.4	11.0	2.4
13	16.4	16.8	0.4
14	20.1	19.1	1.0
15	2.5	3.1	0.6
16	18.5	18.2	0.3
17	18.1	15.5	2.6
18	5.7	7.5	1.8
19	0	0	0
20	0	0	0
21	22.8	24.8	2.0
22	14.8	13.6	1.2
23	23.2	20.3	2.9
24	4.2	5.0	0.8
25	14.2	18.0	4.2

Method. The method employed by us at present in the performance of this test is identical with that previously described,[8,9] except in the final step, where the percentage of retention of the injected pigment is determined by matching the plasma against a series of standards. A total amount of bilirubin* equal to 1 mg. per kilogram of body weight (never is more than 70 mg. used) is dissolved in 15 cc. of a $\frac{1}{10}$ molar solution of sodium carbonate which has been previously brought to the boiling point and then allowed to cool to 80° C. The bilirubin dissolves completely and a clear iodin-colored solution is obtained. A control sample of oxalated blood is collected in a dry syringe to prevent hemolysis, and with the needle *in situ*, the bilirubin is then injected intravenously. Oxalated samples of blood are obtained from the other arm within 5 minutes and again 4 hours after the injection. The concentration of the bilirubin in the plasma is determined by means of the Ernst and Förster[10] method. The plasma is precipitated by redistilled acetone, which is used in different concentrations, depending on the amount of bilirubin in the sample. Thus, with the control and with the sample taken after 4 hours, 2 cc. of acetone and 2 cc. of plasma are used while to 1 cc. of plasma of the specimen taken after 5 minutes, 4 cc. of acetone are added. After the plasma and acetone mixtures are shaken, the samples are centrifuged, filtered, and promptly matched against the standards. Except during actual readings, the acetone

* Bilirubin may be obtained from the Eastman Kodak Company at Rochester, New York, and from Hoffman-LaRoche, Nutley, N. J.

solution of bilirubin must be protected from the light. The final calculations are made as follows:

$$\begin{aligned} &\text{A (control specimen)} \times 2 \text{ (dilution)} = A' \\ &\text{B (5-minute specimen)} \times 5 \text{ (dilution)} = B' \\ &\text{C (4-hour specimen)} \times 2 \text{ (dilution)} = C' \end{aligned}$$

$$\frac{C' - A'}{B' - A'} \times 100 = \text{percentage retention of bilirubin.}$$

The standards* are prepared by making dilutions of potassium dichromate varying from 1 to 2000 to 1 to 10,000, a 1 to 2000 solution yielding a color identical with that of 1 mg. % of circulating bilirubin while a 1 to 10,000 equals 0.2 mg. %. Dilutions between these two extremes are made as follows:

$$\frac{1}{2000} = 1.0 \qquad \frac{1}{2857} = 0.7 \qquad \frac{1}{5000} = 0.4$$

$$\frac{1}{2222} = 0.9 \qquad \frac{1}{3333} = 0.6 \qquad \frac{1}{6666} = 0.3$$

$$\frac{1}{2500} = 0.8 \qquad \frac{1}{4000} = 0.5 \qquad \frac{1}{10{,}000} = 0.2$$

If a drop of hydrochloric acid is added to each standard tube, the tube may be kept indefinitely without fear of change in color. A retention of over 5% of the injected pigment at 4 hours is considered abnormal.

Care should be taken to avoid overheating the sodium carbonate solution, since thus a rather strongly alkalin solution is produced which may cause an uncomfortable reaction. In our experience in over 150 instances, this accident occurred twice. In both instances the patient complained of nausea and hot flushes. The reaction subsided after a few minutes. Proper caution must also be exercised to inject the material intravenously. Accidental extravasation into the surrounding soft parts produces localized pain, edema and tenderness, and, rarely, pyrexia. The constitutional reaction which occurred once in our experience subsided without residue within 48 hours. However, with such a weakly alkalin solution no sloughing occurs.

Summary. 1. The superiority of intravenously injected bilirubin as a means of determining the excretory hepatic function in cases where the serum bilirubinemia is not in excess of 1 mg. % has been pointed out. It seems to be more sensitive than any available single method for determining hepatic dysfunction.

2. The method has been further simplified by the preparation of standards in lieu of the colorimeter.

3. Its indications, precautionary measures and complications have been mentioned.

REFERENCES.

1. Eilbot, W.: Funktionsprüfung der Leber mittels Bilirubinbelastung, Ztschr. f. klin. Med., **106**, 529, 1927.

* The LaMotte Chemical Products Company of Baltimore has prepared a series of these standards for clinical use.

2. Harrop, G. A., Jr., and Barron, E. S. G.: The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, J. Clin. Invest., **9**, 577, 1931.
3. Soffer, L. J.: Present Day Status of Liver Function Tests, Medicine, **14**, 185, 1935.
4. Greene, C.: Discussion, Rose Bengal Test for Liver Function, J. Am. Med. Assn., **85**, 946, 1925.
5. Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, Ibid., **84**, 1112, 1925.
6. Klein, R. I., and Levinson, S. A.: Removal of Bromsulphalein From the Blood Stream by the Reticulo-endothelial System, Proc. Soc. Exp. Biol. and Med., **31**, 179, 1933.
7. Kanner, O.: Ueber die Rolle der Kupfferschen Sternzellen beim Ikterus, Klin. Wchnschr., **3**, 108, 1924.
8. Soffer, L. J.: Bilirubin Excretion as a Test of Liver Function During Normal Pregnancy, Bull. Johns Hopkins Hosp., **52**, 365, 1933.
9. Soffer, L. J., and Paulson, M.: Residual Hepatic Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test, Arch. Int. Med., **53**, 809, 1934.
10. Ernst, Z., and Förster, J.: Ueber die Bestimmung des Blutbilirubins, Klin. Wchnschr., **3**, 2386, 1924.

HEPATIC INFARCTION IN MYELOGENOUS LEUKEMIA AND PERIARTERITIS NODOSA.

By David R. Morgan, M.D.,
Assistant Professor of Pathology, Jefferson Medical College,
Marshall M. Lieber, M.D.,
Instructor of Pathology, Jefferson Medical College,
and
Harold L. Stewart, M.D.,
Assistant Professor of Pathology, Jefferson Medical College,
Philadelphia, Pa.

(From the Pathological Laboratories of the Jefferson Medical College and Hospital of the Jefferson Tumor Clinic, and the Philadelphia General Hospital.)

The object of this communication is to report 2 cases of hepatic infarction recently observed at autopsy. One of these occurred as a terminal complication of myelogenous leukemia, and is perhaps the only reported example of this lesion associated with leukemia. The other occurred in a case of periarteritis nodosa involving the hepatic arterial tree. The mechanical factors operating in the vascular bed of the liver in periarteritis nodosa, will be analyzed and discussed together with the resulting acute and chronic effects on the hepatic parenchyma. Various features of hepatic infarction, reviewed in recent articles by Lund, Stewart and Lieber[1] and by Pass,[2] will be referred to only briefly, as they concern the cases under consideration.

Case Reports. Case 1 (Jefferson Hosp. 1-534).—A. B., a white female, aged 30, was admitted to the hospital January 28, 1935 with myelogenous leukemia. The blood count showed a moderate grade of secondary anemia and 398,000 white blood cells per c.mm. of which 24% were myelocytes. The Wassermann and Kahn reactions on the blood serum were negative. The patient received attention in the hospital and in the out-patient depart-

ment. She responded fairly well to Roentgen ray therapy over the long bones during a period of 2 years. The spleen gradually enlarged to form a hard tender mass extending from the left costal margin to the symphysis pubis and 6 cm. to the right of the midline at the level of the umbilicus. According to the clinical record the liver was never palpated and there was no note regarding tenderness. She developed bronchopneumonia with pleuritis and died March 10, 1935.

Autopsy (14 hours postmortem): *Combined gross and microscopic diagnoses:* 1, chronic myelogenous leukemia; 2, leukemic infiltration and enlargement of spleen and liver; 3, hyperplasia of bone marrow; 4, bronchopneumonia with acute pleuritis, right lower lobe; 5, thrombosis of the mural endocardium of left ventricle and of the pulmonary splenic renal and hepatic vessels; 6, infarction of the liver, lung, spleen and kidney.

The *liver* weighed 3180 gm. and was uniformly enlarged. It was firm, pale, yellowish-brown and friable in consistency. The normal markings were not visible. Several firm, slightly elevated areas were palpable beneath the capsule. On section these areas were dark reddish-brown and sharply defined. They varied somewhat in shape but were roughly rectangular; the largest measured 4 cm. in greatest length. There was extensive occlusion of the veins by soft gray, friable thrombi. Gross exploration of the branches of the hepatic artery showed no evidence of occlusion. It was impossible to distinguish between the small arteries and the veins. The gallbladder contained a few cc. of colored bile and the bile ducts were patulous.

In the microscopic sections from the non-infarcted portion of the liver, thrombi were observed in approximately half the branches of the portal and hepatic veins and in a few of the sinusoids. The majority of the thrombi were fresh; others were liquefied in the center and organized around the periphery and a few were fibrosed and canalized. In this portion of the liver no thrombi were present in the central veins or in the branches of the hepatic artery. Myeloid and erythropoietic cells and megakaryocytes were numerous in the inner third of the hepatic lobules and in lesser numbers in the portal areas which were dense and fibrous (Fig. 1). The patent venous channels were dilated and filled with leukemic cells. The hepatic cells were degenerated and compressed in the inner portion of the lobule but were well preserved elsewhere.

The infarcts and immediately adjacent tissue showed thrombi in the veins as described above together with hyalinized structureless thrombi in several large intrahepatic branches of the hepatic artery. The infarcts were composed of confluent necrotic areas with four fairly distinct zones presenting minor variations in different areas. The central area of the infarct was pale, necrotic and coagulated (Fig. 2). Totally necrotic portal radicles and thrombosed branches of the hepatic artery and portal and hepatic veins were identified within this central area. The cords of necrotic hepatic cells were shrunken, granular and vacuolated and the sinusoidal spaces were widened. They contained imperfectly staining fibrin, outlines of hemolyzed erythrocytes and necrotic leukemic cells. Outside the central area the sinusoids contained a large amount of acidophilic granular débris together with basophilic nuclear particles. More peripherally there were many well preserved red blood cells in the tissue spaces and the sinusoids were filled with masses of well stained fibrin. This entire area was sharply demarcated from the surrounding tissue by an intense infiltration of neutrophils and actively phagocytosing mononuclears which filled the spaces formerly occupied by liver cords.

There was evidence of active regeneration in the surrounding parenchyma. The nuclei were enlarged, hyperchromatic and often multiple and several were observed in mitosis. The superficial areas of infarction were usually separated from the capsule of the liver by a narrow zone of viable hepatic cells and the overlying peritoneum was occasionally covered by an exudate.

SUMMARY—CASE 1. In the liver of a subject dead of myelogenous leukemia several fresh infarcts were found associated with thrombosis of the intrahepatic branches of the hepatic artery, portal vein and hepatic vein. The venous thrombosis was as extensive in the liver generally as in the areas of infarction. It was impossible to state whether the arterial occlusion was the result of embolism or thrombosis. Thrombi in the left ventricle of the heart and in the pulmonary veins constituted a possible source for emboli. On the other hand, occlusion of the hepatic artery may have resulted from widespread thrombosis which was a striking feature of this case.

CASE 2 (P. G. H. 28699).—C. M., white male, aged 44, entered the hospital December 30, 1934 with cyanosis and pain in the abdomen and extremities of a month's duration. There was a history of exposure to lead over a period of years and the patient had been treated for lead colic in 1920. The blood pressure was 200 systolic and 100 diastolic. The urine contained albumin, casts and sugar. The Kahn and Wassermann reactions on the blood serum were negative. There was moderate secondary anemia; the icterus index was 6 and the van den Bergh reaction was indirect negative. An exploratory laparotomy and cholecystostomy were performed January 4, 1935. The gall bladder was thickened and adherent to the under surface of the liver. The head of the pancreas was about 12 cm. in diameter, and the surface showed small areas of fat necrosis. Following operation the drainage bile was blood-stained, and purulent material was aspirated from the gall bladder. Death occurred 5 days after the operation.

Autopsy (1 hour after death): *Combined gross and microscopic diagnoses:* 1, periarteritis nodosa with diffuse proliferative, necrotic, inflammatory and thrombotic arterial lesions and multiple infarcts of the liver, gall bladder, pancreas, brain and adrenal glands; 2, chronic periportal hepatitis with parenchymal degeneration of the liver; 3, chronic cholecystitis with fibrinous serositis; 4, chronic interstitial pancreatitis and fat necrosis; 5, myocardial degeneration; 6, nephrosclerosis and nephrosis.

The *liver* weighed 1800 gm. There were several yellow gray and red areas, approximately 2 cm. in diameter, beneath the capsule in the anterior and inferior portions of the right lobe. On section, these areas were conical with the base directed toward the surface. Some were fibrous, others firm and cheesy and in a few the central areas contained yellowish liquified material.

The gall bladder measured 2.5 cm. in diameter, the wall 0.6 cm. in thickness; it contained a small quantity of purulent material. The mucosa was bright red and covered by a pyogenic membrane. Attempts to probe the cystic duct were unsuccessful. The other bile ducts including the ampulla of Vater were patulous.

Microscopically, the infarcts consisted for the most part of confluent nodules of necrosis with central pale areas surrounded and separated from each other by zones of inflammatory reaction (Fig. 3). The central area of infarction was well circumscribed and showed total coagulation necrosis with preservation of the structural outlines of all the tissue elements. The hepatic cells were shrunken and presented sharply outlined faintly basophilic nuclei embedded in pale granular, acidophilic cytoplasm containing small clusters of brown pigment granules. The bloodvessels contained acidophilic material resembling fibrin and the sinusoids were variously filled with imperfectly stained débris. Outside the central area cellular disintegration was pronounced, the sinusoids were packed with mono-

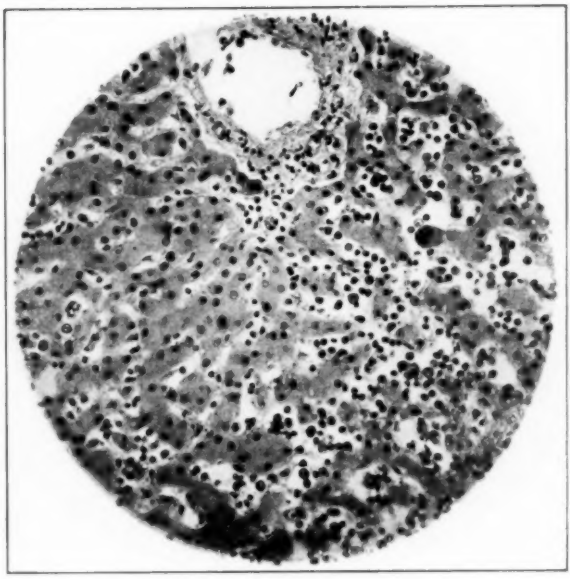


FIG. 1.—Liver. Case 1. Showing non-infarcted area with leukemic cells. (× 250.)

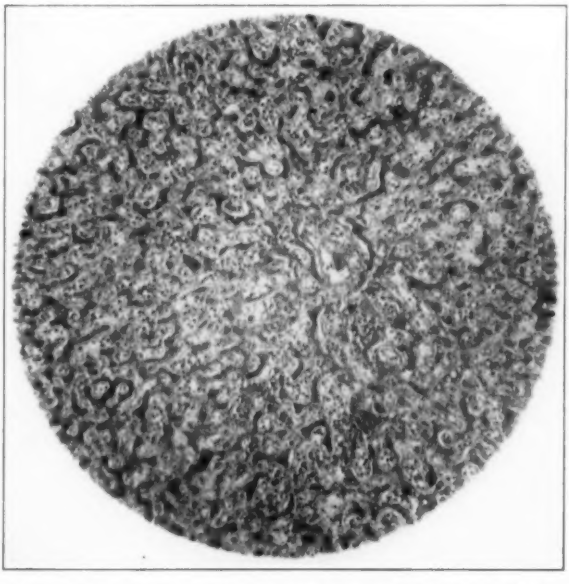


FIG. 2.—Liver. Case 1. Showing total necrosis of all tissue elements in area of infarction. The outlines of the leukemic cells are visible. (× 100.) Contrast with Fig. 1.

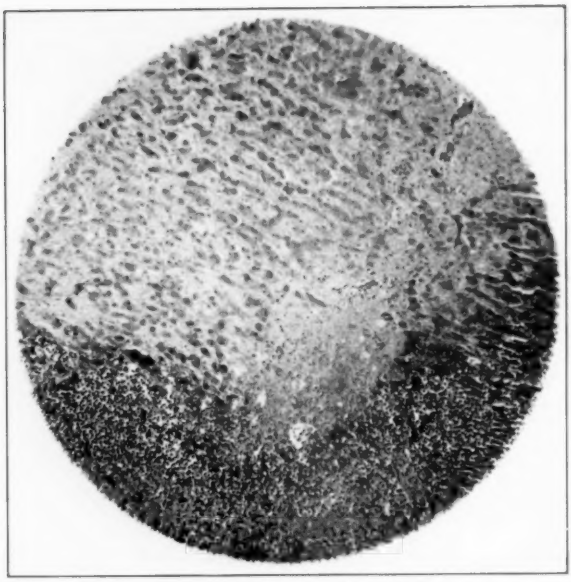


FIG. 3.—Liver. Case 2. Portion of infarct with pale central area and bordering zone of inflammatory cell infiltration. (× 100.)

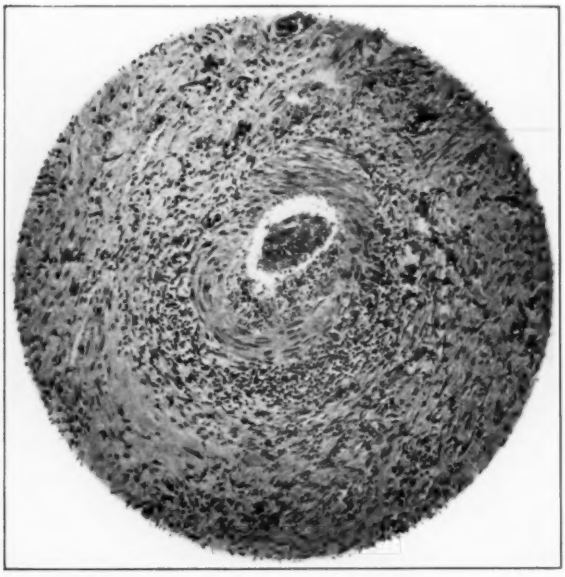


FIG. 4.—Branch of hepatic artery (Case 2) showing thrombosis and inflammatory changes of periarteritis nodosa. (× 100.)

nuclear leukocytes and neutrophils and there was a large amount of basophilic nuclear material. This was surrounded by a zone showing a chronic proliferative reaction which blended superficially with Glisson's capsule. This area was composed of edematous granulation tissue, inflammatory cells, small proliferating tubular structures resembling bile ducts and scattered groups of viable hepatic cells.

Similar proliferative changes were noted throughout the liver generally, and many of the portal radicles were enlarged and fibrotic. In some areas, the picture resembled that of cirrhosis. Several large branches of the portal vein were thrombosed and fibrotic. The branches of the hepatic artery showed the characteristic changes of periarteritis nodosa with thrombosis of the lumen and necrosis and nodular areas of inflammatory reaction in and around the walls of these vessels (Fig. 4). The hepatic parenchyma not involved in the gross nodules of infarction was congested and contained microscopic areas of necrosis in parts of single and adjacent lobules.

SUMMARY—CASE 2. In a case of periarteritis nodosa, fresh, organized, bland and liquefied infarcts of the liver were observed in relation to occluded branches of the hepatic artery and portal and hepatic veins. There were also cirrhotic changes throughout the remainder of the organ.

Comment. The lesions which occur in the liver with periarteritis nodosa show marked variability in their morphology. The literature contains a number of reports of hepatic necrosis developing by this mechanism and certain of these fulfill all the requirements of genuine infarction. Arkin[3] states that the presence of multiple infarcts in the liver in the absence of endocarditis should always call to mind periarteritis nodosa of the hepatic artery, and Pass[2] believes this condition to be the most common single cause of hepatic infarction. The finer ramifications of the arteries of the liver terminate as "end-arteries" within the substance of the organ and the collateral circulation of these vessels is extremely limited. Since the life of the hepatic cell is dependent upon an adequate supply of arterial blood, partial or complete occlusion of these vessels is followed by regressive changes of varying degrees.

Five cases of hepatic infarction in typical form occurring in periarteritis nodosa were found in the literature (Versé,[4] Versé,[5] Vance and Graham,[6] Gellerstedt and Wennerberg[7] and Pass). In 10 other cases, lesions of the liver grossly interpreted as infarcts were reported (Christeller,[8] Cases 2 and 3; Blum;[9] Arkin, Case 3; Jäger;[10] Weigeldt;[11] Kroetz;[12] Baló,[13] Case 1; Harbitz;[14] and Krahulik, Rosenthal and Loughlin.[15] However, in the absence of detailed microscopic evidence, this diagnosis may be questioned. In 6 additional cases examined microscopically, none presented the characteristics of true infarction although their gross appearance was suggestive. These cases are of interest and may be cited briefly. In Longcope's[16] case there were irregular, well outlined, slightly depressed red patches 0.5 to 2 cm. in diameter scattered over the cut surface of the liver from the periphery to the hilus. Microscopically these areas showed congestion and localized areas of

neutrophil infiltration. The liver cells were swollen and exceedingly granular. There were a few small foci of necrosis, with two or three vacuolated liver cells, granular and infiltrated with neutrophils. Marinesco[17] described intense vascular lesions along the ramifications of the hepatic artery with small zones of fatty degeneration in the parenchyma. In Cameron and Laidlow's[18] case "white infarcts" 4 by 3 cm. were found in the left lobe; microscopically these consisted of shrunken liver cells which were atrophic but not necrotic. The nuclei although imperfect in shape and staining, were fairly well preserved. Arkin's Cases 2 and 4 contained many irregularly outlined, reddish depressed areas; microscopically the liver parenchyma was destroyed leaving behind a vascular network filled with blood. In Mönckeberg's[19] case, the cells in the periphery of the lobules were normal, those in the centers were fatty, degenerated and necrotic with infiltrated neutrophils. From the histologic data of the 6 cases just cited, it appears that none of these lesions should be regarded as true hepatic infarctions.

Chronic lesions of a diversified character also occur in combination with or independent of acute lesions, such as inflammation in and about the arteries, stasis, anemia, hemorrhage from rupture of an aneurysm (Friedberg and Gross[20]), sinusoidal thrombosis and hepatic cell atrophy. The end results are fibrosis of the capsule, branched, diffuse or circumscribed fibrous scars corresponding to narrowed and obliterated arteries, perilobular and intralobular fibrosis, chronic interstitial hepatitis (Christeller, Case 2; Baló, Case 3; Elizalde and Di Pietro[21]; Friedberg and Gross); and in Arkin's Case 5, "hepar lobatum." This latter case is of particular interest. Four years prior to death the patient developed an acute attack of jaundice. At autopsy changes interpreted as late or healed periarteritis nodosa were found. The liver was small, coarsely granular and showed a number of deeply penetrating, depressed scars over which the capsule was wrinkled. The cut surface was traversed by connective tissue septa containing nodular, thickened and obliterated branches of the hepatic artery. Microscopic examination disclosed areas of unchanged liver tissue side by side with areas of marked congestion from which the parenchyma had disappeared. Arkin believed that the hepatic lesion was the result of periarteritis rather than the healed stage of yellow atrophy of the liver.

A number of mechanical factors influence the hepatic changes in periarteritis nodosa. Vascular occlusion may be abrupt or gradual, complete or incomplete in a single arterial branch. When gradual, sufficient time may elapse for the development of a collateral circulation but, during the interval, the parenchyma may suffer varying degrees of damage. Sudden complete occlusion by embolism or thrombosis may occur in a branch of the hepatic artery which was previously normal or was the seat of an incomplete occlusion the result of periarteritic lesions or aneurysm formation. A source for

emboli in such cases may exist locally in the proximal arterial tree or they may arise from thrombi in the pulmonary veins or left heart. Additional factors contributing to the production of vascular lesions in the liver of periarteritis nodosa are thrombosis of the branches of the portal and hepatic veins which is a common feature in this condition. In view of these factors the occurrence of diffuse, focal or intralobular necrosis, localized areas of congestion and hemorrhage and hepatic cell atrophy is readily understood. This also explains those changes described by some authors which are characterized by disappearance of hepatic cells in limited areas leaving behind a network of dilated sinusoids. This latter lesion, in various stages, resembles the "atrophic red infarct of Zahn" and the red areas described by Marchand in multiple nodular hyperplasia (subacute atrophy of the liver).

Infarcts of the liver occurring in periarteritis nodosa are frequently localized in areas already the seat of a well developed inflammatory reaction with its complicated enzymatic response. The action of heterolytic enzymes within these areas of necrosis may produce liquefaction, so that centers of infarcts may disintegrate with the formation of pus. The chronic hepatic lesions result, in part, from repair following inflammation along the bloodvessels, about infarcts, and in focal areas within the lobule. Fibrosis may also result from parenchymal changes produced by the pressure of aneurysms or periarteritic nodules. The progressive development of this combination of diversified changes may eventuate in a finely or coarsely granular liver with depressed scars on the surface not unlike that seen in cirrhosis.

Conclusions. 1. Two cases of hepatic infarction are described and illustrated. These occurred respectively in chronic myelogenous leukemia and in periarteritis nodosa.

2. A summary of the hepatic lesions occurring in the reported cases of periarteritis nodosa is presented and discussed, together with an analysis of the factors operating in the vascular bed of the liver and of the resulting effects on the parenchyma.

3. Periarteritis nodosa is the most frequent single cause of hepatic infarction.

4. The later stages of the necrotic and inflammatory processes of periarteritis nodosa resemble other cirrhotic processes.

REFERENCES.

1. Lund, H., Stewart, H. L., and Lieber, M. M.: Hepatic Infarction, Am. J. Path., **11**, 157, 1935.

2. Pass, I. J.: Infarction of the Liver, Ibid., **11**, 503, 1935.

3. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa, Ibid., 6, 401, 1930.

4. Versé, M.: Periarteriitis nodosa und Arteriitis syphilitica cerebralis, Beitr. z. path. Anat. u. z. allg. Path., **40**, 409, 1907.

5. Versé, M.: Ueber totale Pfortaderobliteration und anämische Infarkte der Leber, Verhandl. d. deutsch. path. Gesellsch., **13**, 314, 1909.

6. Vance, B. M., and Graham, J. E.: Periarteritis Nodosa Complicated by Fatal Intrapericardial Hemorrhage, Arch. Path., **12**, 521, 1931.
7. Gellerstedt, W., and Wennerberg, B.: Zwei Fälle von Periarteriitis nodosa, Upsala, Läkaref. Förh., **40**, 95, 1934.
8. Christeller, E.: Ueber die Lokalizationen der Periarteriitis nodosa, besonders in den Bauchorganen, Arch. f. Verdauungskr., **37**, 249, 1926.
9. Blum, K.: Zur Klinik der Periarteriitis nodosa, Wien. klin. Wchnschr., **42**, 40, 1929.
10. Jäger, E.: Zur histologischen Ausheilung der Periarteriitis nodosa und deren Beziehung zur juvenilen Atherosklerose, Virch. Arch. f. path. Anat., **288**, 833, 1933.
11. Weigeldt, W.: Klinische Beiträge zur Periarteriitis nodosa, Deutsch. Ztschr. f. Nervenh., **100**, 260, 1927.
12. Kroetz, C.: Zur Klinik der Periarteriitis nodosa, Deutsch. Arch. f. klin. Med., **135**, 311, 1921.
13. Baló, J.: Ueber eine Haüfung von Periarteriitis-nodosa-Fällen, nebst Beiträgen zur Polyneuritis infolge von Periarteriitis nodosa, Virch. Arch. f. path. Anat., **259**, 773, 1926.
14. Harbitz, F.: Different Forms of Arteritis, Especially "Periarteritis nodosa," Internat. Clin., **1**, Ser. 37, 130, 1927.
15. Krahulik, L., Rosenthal, M., and Loughlin, E. H.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood with Meningeal Involvement, Am. J. Med. Sci., **190**, 308, 1935.
16. Longcope, W. T.: Periarteritis Nodosa, with Report of a Case, with Autopsy, Bull. Ayer Clin. Lab., Penna. Hosp., **5**, 1, 1908.
17. Marinesco, M. G.: Contribution a l'étude de la maladie de Kussmaul (périartérite noueuse), Bull. Acad. de méd. Paris, **90**, 289, 1923.
18. Cameron, H. C., and Laidlow, P. P.: A Case of Periarteritis Nodosa, Guy's Hosp. Rep., **69**, 159, 1918.
19. Mönckeberg, J. G.: Ueber Periarteriitis nodosa, Beitr. z. path. Anat. u. z. allg. Path., **38**, 101, 1905.
20. Friedberg, C. K., and Gross, L.: Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, Arch. Int. Med., **54**, 170, 1934.
21. Elizalde, P. I., and Di Pietro, A.: Periarteritis nudosa (Enfermedad de Kussmaul Maïer), Rev. Asoc. méd. argent., **48**, 1195, 1934.

THE EFFECT OF OIL OF WINTERGREEN ON THE INCIDENCE OF SPONTANEOUS CARCINOMA IN MICE.*

IV. Effect on Growth Rate and Survival Time after Onset of Malignancy.

By Leonell C. Strong, Ph.D.,
Assistant Professor of Anatomy, Yale University School of Medicine, New Haven, Conn.

(From the Department of Anatomy, Yale University School of Medicine.)

Recently data were published[1,2,3] which indicated that the true oil of wintergreen had a significant effect on survival time of mice harboring spontaneous cancer of the mammary gland. It was shown that if such mice had received daily small amounts of the oil in an otherwise standard oatmeal diet, they would live longer than their controls. This effect on survival time was cumulative;

* This experiment has been made possible by grants from the Josiah Macy, Jr., Foundation and the International Cancer Research Foundation. Acknowledgment is also given to Dr. A. H. Smith for his kindness in redistilling the commercial synthetic methyl salicylate (Eimer and Amend) used in this investigation. Dr. L. D. Francis determined that the oil weighed, on an average, 0.2265 gm. per drop (by medicine dropper).

that is, the longer the animal had been on the oil-oatmeal diet or the younger it had been placed on that régime, the longer it would live after the ensuing tumor had developed.

In order to test out further the action of the various components of the natural oil of wintergreen on malignancy, it became desirable to try the redistilled synthetic methyl salicylate on cancerous mice after they had developed spontaneous carcinomas of the mammary gland. For this study 32 mice of the A strain[4] were employed. These were divided into three experimental groups and two control groups, according to Table 1.

TABLE 1.—SURVIVAL TIME OF MICE.

	No. of mice.	Average survival time in days.
1:1 MS	4	41.5
First control	7	51.8*
1:2 MS	7	54.7
Second control	7	59.3
1:3 MS	7	56.6

* One control animal lived 154 days of life after the onset of malignancy. For reasons given in the text, the calculation of survival time (prognosis) for the first group of controls is given on the basis of the 6 other mice used.

Four criteria of the possible effect of the oil on the tumor-host relationship was used. These were: 1, the growth rate of the tumor; 2, food intake; 3, total body weight; and 4, the survival time after the discovery of the tumor. All animals were kept under the same conditions. A single animal was kept in a cage. Food was given in a round glass dish over which was clamped a metal cover. A single hole approximately $1\frac{1}{4}$ inches in diameter had been punched in the center of the metal cover. The basic diet for the control animals was a mixture of Quaker rolled oats, Baugh and Sons best meat scrap, Klim powdered "gas packed" whole milk, and salt. The oil was added to this basic diet in three proportions. In the first experimental group, the oil was added in the ratio of 1 drop of oil (by medicine dropper) to 1 gm. of the oatmeal mixture (1:1 MS, Table 1). In the second experimental group the ratio of 1 drop to 2 gm. of food was used (1:2 MS, Table 1), and in the third group the ratio of 1 drop to 3 gm. of the oatmeal mixture was employed (1:3 MS, Table 1). The two groups of controls were alternated between the experimental groups in order to avoid undue sampling of mice with spontaneous tumors.

The results are given in a series of charts. Chart 1 gives the data on the growth rate of the tumors in the two control groups. These growth rates are calculated on the basis of the linear measurement, determined by calipers, along the greatest diameter. Measurements on the other two dimensions had also been taken but since these showed the same tendency, they are not included in this report. It does not seem desirable to attempt to reconstruct the size of the

tumor by taking into consideration the three dimensions at one time. Necrosis and hemorrhage into the tumor always interferes with determination of absolute size in the growing tumor.

Chart 1 shows that the growth rates for the two sets of controls are identical. For this reason, the two groups of controls are added together, as is shown by the solid line in Chart 3.

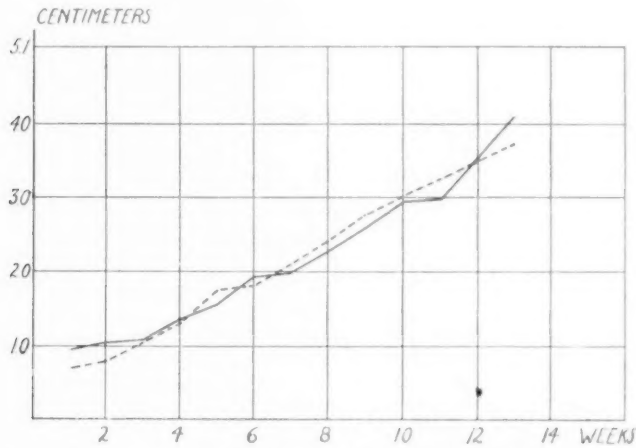


CHART 1.—GROWTH RATES OF TUMORS OF CONTROL MICE determined by linear measurement across the greatest diameter. Time in weeks is along the base line; linear measurement of the tumors in centimeters is given along the vertical line. Average growth rate of tumors for first group of controls is given on the solid line; the average growth rate for the second group of controls is given on the dash line.

Chart 2 gives the data on the growth rates (greatest linear diameter) for the tumors in the three sets of experimental (oil-treated) animals. The first group (1:1 MS) is given on the solid line; second group (1:2 MS) on the short dash line; while the third group (1:3 MS) is given on the dot and dash line. Since the rate of increase for the three groups is the same, we decided to add all experimental animals together. The difference between the three groups lies in the size difference of the tumors at the start of the experiment. The three experimental curves are added together and the resultant curve is given on the dash line of Chart 3.

Chart 3 gives the comparative data on tumor growth rates for the control and the experimental animals. For the first 8 weeks of growth the two curves are parallel, the experimental curve is slightly above the control group. This is due to the fact that the experimental mice had slightly larger tumors at the start of the experiment. Beyond 8 weeks, the curve for the experimental animals drops below that for the control mice.

Chart 4 gives the data on total body weight throughout the observation period. The data for the control animals are given on

the solid line; comparable data for the experimental animals are given on the dash line. It is seen that the control animals gradually increased in weight during the extent of the experiment; whereas

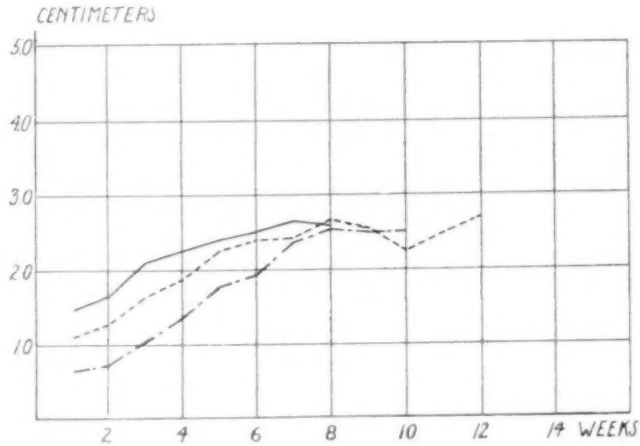


CHART 2.—GROWTH RATES OF TUMORS OF TREATED MICE. The first group of experimental animals (1:1 MS) is given on the solid line; the second group (1:2 MS) along the dash line, while the third group (1:3 MS) is given along the dot and dash line. Time in weeks is given along the base line; lineal measurement of tumor in centimeters is given on the vertical line.

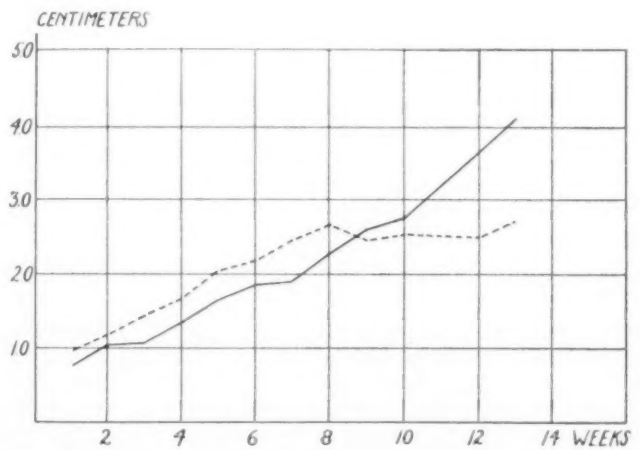


CHART 3.—COMPARATIVE DATA ON GROWTH RATES OF TUMORS. The control group is given on the solid line and the averaged three experimental groups on the dash line.

the experimental animals lost weight for the first 4 weeks. After that time the curve for the experimental group increased parallel to the control curve.

An attempt was made to ascertain the cause of the loss of weight on the part of the experimental group during the first 4 weeks. The first suggestion that seemed reasonable was the fact that the bitterness of the food (with the added oil of wintergreen) prevented the animal from eating sufficient quantities to sustain a standard body weight. Accurate determinations on the daily consumption of food for the experimental animals were obtained. For the first 2 weeks, this average food intake per mouse was 4.30 gm. per day; for the second 2 weeks it was 4.87 gm. per day; for the third 2-week period it was 4.41 gm. per day, and for the fourth 2-week period it was 5.25 gm. per day.

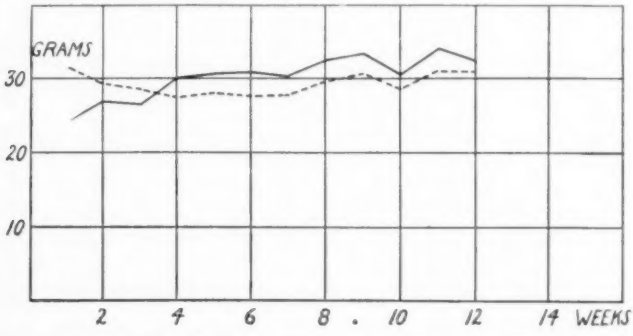


CHART 4.—TOTAL BODY WEIGHTS (MOUSE PLUS TUMOR). The control mice are given on the solid line; the experimental animals on the dash line. Time in weeks is given along the base line, weight in grams is plotted along the vertical line.

Comparable data for the control group was not available. With the equipment at hand, the control animals spilled so much food, that reliable data were not possible. It seems unlikely, however, that the administration of the oil interfered in the normal food eating habits of the mice.

Charts 5, 6, and 7 present the data on survival times of the mice after the onset of cancer for the experimental and control animals. Chart 5 gives the data for the control animals. For the first set of controls, the data are on the solid line; for the second group of controls the data are on the dash line. Since there is little difference between the two groups, the data are added together. The data for the combined control animals thus gave the curve on the dot and dash line. This average curve is also given on the solid line of Chart 7.

Chart 6 gives the data on the survival time for the second and third groups of experimental animals. Since only four animals comprised Group 1, a survival curve for this number is not significant. The average for the curves for the two groups of experimental animals is given on the dash line of Chart 7.

In the control groups was one animal that lived 154 days. Such an animal is extremely rare among the tumor mice of the inbred

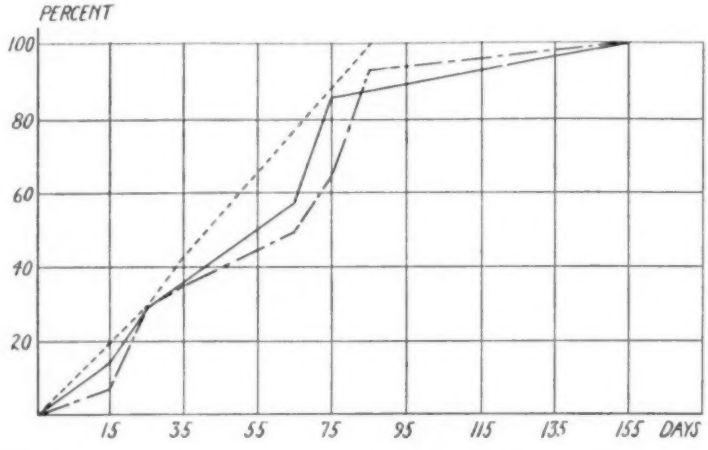


CHART 5.—SURVIVAL TIME OF MICE WITH SPONTANEOUS CONTROL TUMORS. The first group of controls is given on the solid line, the second group on the dash line. The average for the two groups is given on the dot and dash line. Time in days is plotted along the base line; percentage of dead mice is given on the vertical line. Successive points on the curves are therefore cumulative.

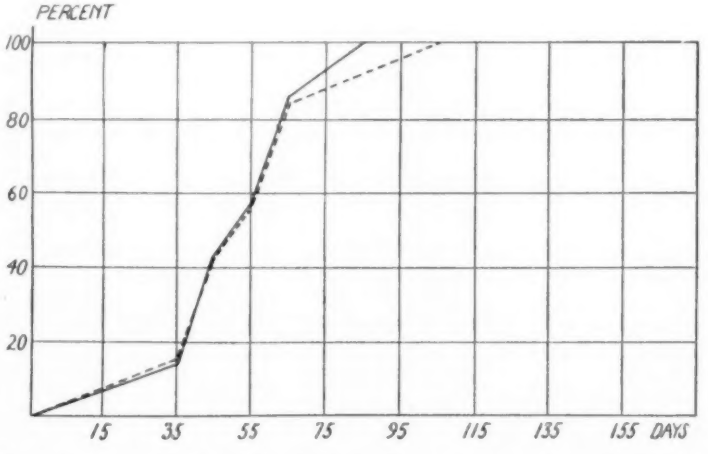


CHART 6.—SURVIVAL TIME (PROGNOSIS) FOR TWO SETS OF EXPERIMENTAL ANIMALS. Time in weeks is given on the base line; percentage of death is given on the vertical line.

strain used in this experiment. Consequently, we have deemed it wise to exclude it from calculations of survival time. When this is done, it is obvious that there is no difference between the survival

times for the experimental animals and the control groups (see Table 1 and Chart 7).

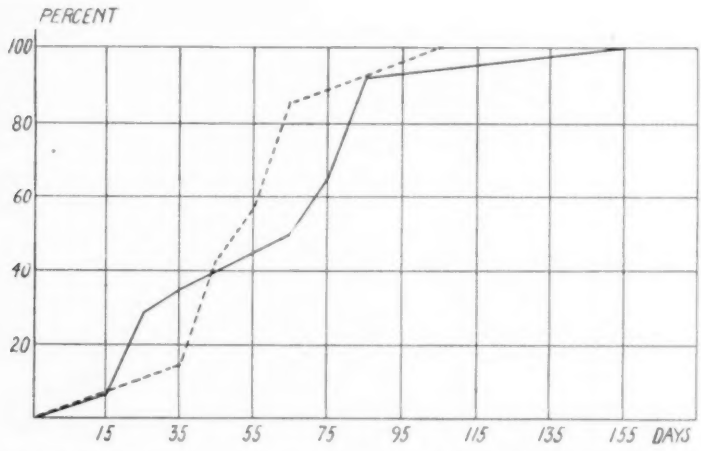


CHART 7.—COMPARATIVE DATA ON SURVIVAL TIME FOR THE TWO GROUPS OF MICE. The average survival time for the controls is given on the solid line; the survival time for the experimental animals is given on the dash line.

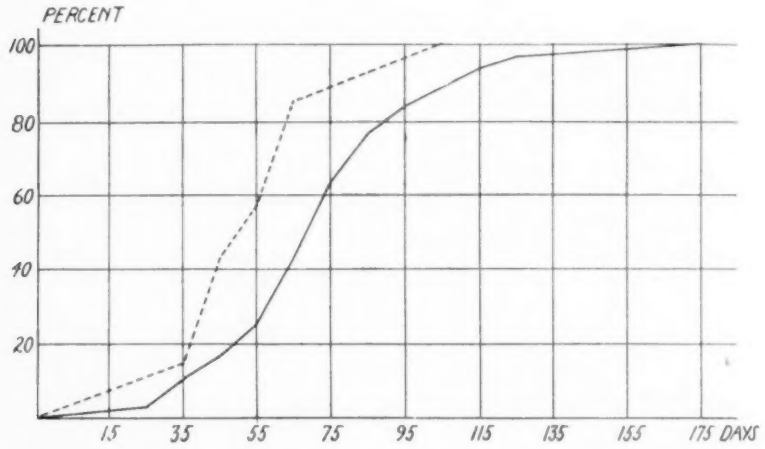


CHART 8.—COMPARATIVE DATA ON SURVIVAL TIMES. Survival times for experimental animals that had received daily small amounts of the natural oil of wintergreen before the onset of malignancy are given on the solid line, and for experimental animals that had been given synthetic methyl salicylate after the onset of the disease on the dash line.

Chart 8 gives (1) the data on the survival time of cancerous mice that have been put on an oil-oatmeal diet after the onset of the disease, and (2) data on the survival time of cancerous mice that had been put on an oil-oatmeal diet before the onset of the disease.[3]

Discussion. The daily administration of small amounts of the natural oil of wintergreen has had two effects on the incidence and severity of spontaneous carcinoma of the mammary gland.[1,2,3] In the first place, the age at which spontaneous carcinoma of the mammary gland occurs has been delayed, and, in the second place, survival time of the animal harboring a tumor is also increased. This applies only to those animals which have been subjected to the treatment over a period of weeks or which were young mice at the start. The present study would indicate that the disease of cancer of the mammary gland cannot be influenced by the daily administration of redistilled synthetic methyl salicylate through the diet when treatment is started after the onset of malignancy. The slowing up of the growth rate of tumors in the experimental animals below the rate for the controls is probably due to earlier mortality of those mice which were growing the tumors at a more rapid rate.

Conclusions. 1. In order to influence malignancy, natural oil of wintergreen must be administered to young animals over a period of weeks before the condition arises.

2. Daily administration of the synthetic oil of wintergreen after the onset of cancer has no detectible effect on malignancy.

REFERENCES.

1. Strong, L. C.: Possible Effect of Oil of Gaultheria in Diet of Mice Susceptible to Spontaneous Carcinoma of the Breast. I. A Suggestion, Proc. Soc. Exp. Biol. and Med., **30**, 386, 1932.
2. Strong, L. C.: Idem. II. A Latent Period? Am. J. Cancer, **20**, 387, 1934.
3. Strong, L. C.: Idem. III. Survival Time, Ibid., **25**, 797, 1935.
4. Strong, L. C.: The Establishment of the A Strain of Inbred Mice, J. Hered. **27**, 21, 1936.

CHRONIC DYSENTERY, DISTAL ILEITIS AND ULCERATIVE COLITIS.

A FOLLOW-UP OF THE JERSEY CITY EPIDEMIC OF BACILLARY DYSENTERY.

BY JOSEPH FELSEN, M.D.,
DIRECTOR OF LABORATORIES AND RESEARCH, THE BRONX HOSPITAL, NEW YORK CITY,

AND

HAROLD GORENBERG, M.D.,
RESIDENT IN GYNECOLOGY, MEDICAL CENTER, JERSEY CITY, N. J.

(From The Bronx Hospital and the Jersey City Medical Center.)

ADEQUATE follow-up studies of acute bacillary dysentery may shed important light upon certain obscure intestinal diseases. With this purpose in mind, and in order to corroborate observations previously made upon sporadic cases, a 9 to 12 months' study was

instituted following the major Jersey City epidemic of 1934.[1] Inasmuch as only hospitalized patients were included in this investigation, centralized control was effected both during the epidemic period and the subsequent follow-up.*

TABLE 1.—CHRONIC SYMPTOMATOLOGY 9 TO 12 MONTHS AFTER AN ATTACK OF ACUTE BACILLARY DYSENTERY.

Total number of cases in original group	210	
Total number of cases in follow-up	122	
Persistent or recurrent symptoms and signs		46 (37.7%)
Diarrhea with blood, mucus and pus	8 (6.5%)	
Watery diarrhea without gross blood	12 (9.8%)	
Bloody evacuations without diarrhea	3 (2.4%)	
Miscellaneous intestinal symptoms	23 (19.0%)	

TABLE 2.—VISIBLE EVIDENCE OF ULCERATIVE COLITIS OR ILEITIS IN FOLLOW-UP OF 122 CASES OF ACUTE BACILLARY DYSENTERY.
(13 Out of 122 Followed Cases.)

(*a*) Roentgenographic evidence of chronic ulcerative colitis	8 (6.5%)
(*b*) Additional cases with sigmoidoscopic evidence of chronic ulcerative colitis	2 (1.7%)
(*c*) Chronic distal ileitis (2 at operation, 1 at necropsy*)	3 (2.5%)

* Almost entire ileum and all of colon involved.

Statistical Study of Chronic Intestinal Symptoms in 122 Cases. Of an original group of 210 patients we were able to secure the return of 122. Approximately 1 out of every 3 patients (37.7%) who were originally studied during the epidemic of 1934 had persisting or recurring symptoms and signs of intestinal involvement (Table 1). Diarrhea persisted in 20 instances (16.3%), 8 patients exhibiting gross evidence of blood, mucus and pus, 12 having watery bowel movements. Three additional patients (2.4%) had mucoid, bloody stools, but the daily frequency was not pronounced. Almost without exception recurring attacks of abdominal cramps were noted in the 23 cases (18.7%) referred to and, in addition, were present as the sole complaint in 8 others (6.5%). Intestinal spasm and tenderness in the right or left lower quadrants were present in almost all of the 46 cases with recurring or persisting symptoms. Roentgenographic evidence of chronic ulcerative colitis was obtained in 8 cases (6.5%) and sigmoidoscopic examination revealed lesions in the rectosigmoid in 2 more (1.7%). In all of the others clinical evidence pointed to lesions higher up in the colon, but permission for further examination could not be obtained. Two additional patients (1.7%) developed chronic distal ileitis with mesenteric lymphadenitis, proven at operation. In one instance the process involved the distal 20 cm. of ileum as well as the cecum and appendix. In the other the distal 40 cm. of ileum was affected. A third case (0.8%) was proven at necropsy. Almost the entire ileum and all

* We are indebted to Dr. George O'Hanlon, Superintendent of the Medical Center, for making these studies possible and to Dr. Louis L. Perkel for his coöperation in the roentgenographic examinations.

of the large bowel was the seat of a diffuse ulcerative lesion with inflammatory polyposis. There was a perforation in the transverse colon.

Discussion of Statistical Data and Their Significance. Leaving out of consideration all cases except those in which corroborative sigmoidoscopic, pathologic or roentgenographic evidence was obtained, it appears that approximately 10% developed chronic distal ileitis or ulcerative colitis by the end of the first year. The clinical and pathologic picture was distinctive and unmistakable and the initial infection was clearly due to B. dysenteriæ (Flexner) in each instance. Careful investigation showed that in every case, although the original attack of acute bacillary dysentery subsided, it had never cleared up completely. The chronic manifestations were definitely a continuation of the original disease. Collateral studies indicate that, while in a certain percentage of these chronic cases B. dysenteriæ may still be recovered after the lapse of a year or more, in the majority of them this organism cannot be found on repeated fecal cultures. It appears, moreover, that secondary intramural invasion by the enterococcus and B. coli occurs through the ulcerations originally caused by B. dysenteriæ. This is associated with chronicity of the disease as, once established, intramural infection is persistent and difficult to eradicate. Pathologically, the intestinal manifestations of acute bacillary dysentery are those of an enterocolitis. Any part of the small or large intestine may be involved, often in a segmental fashion. There is a definite predilection, however, for the distal ileum and colon. The chronic lesions represent unhealed acute lesions both as regards location and pathologic character. Thus, chronic distal ileitis is always preceded by the distal ileitis of acute bacillary dysentery and the chronic ulcerative colitis or granulomatous lesion is the aftermath of a similar antecedent infection in the colon, independent of or concomitant with involvement of the small intestine. As previously noted by one of us (J. F.), the various stages were observed in individual cases from the onset of acute bacillary dysentery to the fully developed ileal or colonic lesion. The follow-up studies in the Jersey City epidemic afford further evidence in support of the common pathogenesis of these diseases.

From the clinical and public health standpoints certain relevant observations are perhaps significant. If chronic distal ileitis and chronic ulcerative colitis are the result of bacillary dysentery, it is quite evident that accurate diagnosis, prompt isolation and adequate treatment are essential. It is important to recognize the atypical forms, such as the appendicular type with acute distal ileitis and mesenteric lymphadenitis, asymptomatic, afebrile, constipated or meningitic. Antidysentery serum of high antitoxin content must be given within the first 24 to 48 hours to be effective. Frequent periodic surveys of all foodhandlers, particularly in institutions,

should be made as well as careful supervision of water and all food supplies.

Conclusion. If one may generalize on the basis of 122 cases of a total of 201 studied during and after a major epidemic, it may be said that in acute bacillary dysentery (Flexner) approximately 90% of the patients recover completely. The other 10% develop the chronic dysentery in the forms more generally known as distal (regional) ileitis or ulcerative colitis. The intractable nature of these diseases suggests that perhaps the most adequate form of therapy is the prevention of bacillary dysentery.

REFERENCE.

1. Felsen, J., Rundlett, E. V., Sullivan, J., and Gorenberg, H.: Atypical Flexner Dysentery: A Preliminary Report of the Jersey City Epidemic, J. Am. Med. Assn., **103**, 1055, 1934.

THE APPEARANCE OF THE ELECTROCARDIOGRAM IN RELATION TO THE POSITION OF THE HEART WITHIN THE CHEST.

By Louis N. Katz, M.D.,
DIRECTOR OF CARDIOVASCULAR RESEARCH, MICHAEL REESE HOSPITAL,
AND
M. Robinow, M.D.,
INTERN, CARDIOVASCULAR DEPARTMENT, MICHAEL REESE HOSPITAL,
CHICAGO, ILL.

(From the Heart Station and the Cardiovascular Laboratory, Department of Physiology, Michael Reese Hospital.)

It has been established that changes in the position of the body lead to changes in the 3 lead electrocardiogram which cannot be satisfactorily explained by the Einthoven equilateral triangle concept.[1,2,3] This we have confirmed in the present study. Further information was obtained by observing the changes in the position of the heart and surrounding structures by Roentgen ray.

Procedure. Standard 3 lead electrocardiograms were taken on 7 normal subjects and 5 patients with right-sided pneumothorax (administered therapeutically for pulmonary tuberculosis).* In addition, various leads over the chest were taken in 3 normal subjects using the left leg as the site of the second electrode as is the practice now in taking Lead IV.

Records were taken with the subjects in the following postures:

1. Lying on the back.
2. Sitting upright.
3. Lying on the right side.
4. Lying on the left side.
5. Lying on the abdomen.
6. Sitting up and leaning forward.
7. Resting on hands and knees.
8. Leaning over the edge of the bed with the head and trunk hanging down vertically.

* We are indebted to Dr. M. Biesenthal for permission to study these latter patients.

With these postures the body was rotated on its sagittal axis, viz. postures 1, 3, 4, 5, and around an axis connecting both hip joints; viz. postures 1, 2, 6, 7, 8 and 5. In 1 of the normal subjects a 6-foot Roentgen ray plate of both the anteroposterior and lateral views was taken in each of the above postures.* The plates were taken with the subject holding his breath at mid-inspiration.

Discussion of Results. In Table 1 is summarized the effect of changing the body posture on the electrical axis. It is evident that the changes are not always consistent and do not coincide with what might be anticipated from the theory of the Einthoven equilateral triangle.

TABLE 1.—SHIFT IN ELECTRICAL AXIS WHEN POSTURE OF SUBJECT IS CHANGED.

Subject	From lying on back to					From lying on right side to		From lying on left side to lying on abdomen.
	Lying on right side	Lying on left side	Lying on abdomen	Sitting upright	Sitting leaning forward	Lying on left side	Lying on abdomen	
Normal								
1. Fri.	L	R		L	L	R		L
2. Ko.	?	R		L	L	R	L	L
3. Bl.	?	R		L	?	R	L	L
4. Fra.	L	R	?		?	R		L
5. Fre.	L	R	R	L	L	R	R	L
6. Ock.	R	R	?		?	?	?	L
7. Dre.	..	R	L	L	R	R	L	L
Having right pneumothorax								
1. Kle.	R	R	R	..	..	..	R	L
2. Hir.	R	R	..	..	..	?	..	L
3. Bag.	R	R	?	L	?	..	L	L
4. Ros.	R	R	L	..	L	..	L	L
5. Hey.	?	?	..	L	..	..	L	L

L = left axis shift (electrical). .. = no significant axis shift (electrical).
R = right axis shift (electrical). ? = questionable axis shift (electrical).

In addition there were changes in voltage independent of axis shift, changes in the *P* wave, in *Q R S* contour and in the *T* wave as the body position changed. The contour and amplitude in the precordial leads also showed marked changes when the posture was altered.

It is obvious that these electrocardiographic changes must be due to changes in the position of the heart in the chest. The Roentgen ray plates (Fig. 1) showed that the position changes were a combination of:

* We are grateful to Dr. R. Arens for placing the facilities of the Roentgen ray Department at our disposal.

1, Rotation around an anteroposterior axis situated at the base of the heart; 2, rotation around a transverse axis situated at the base of the heart; 3, rotations around the sagittal axis of the heart running from the apex to the base; 4, displacement of the heart

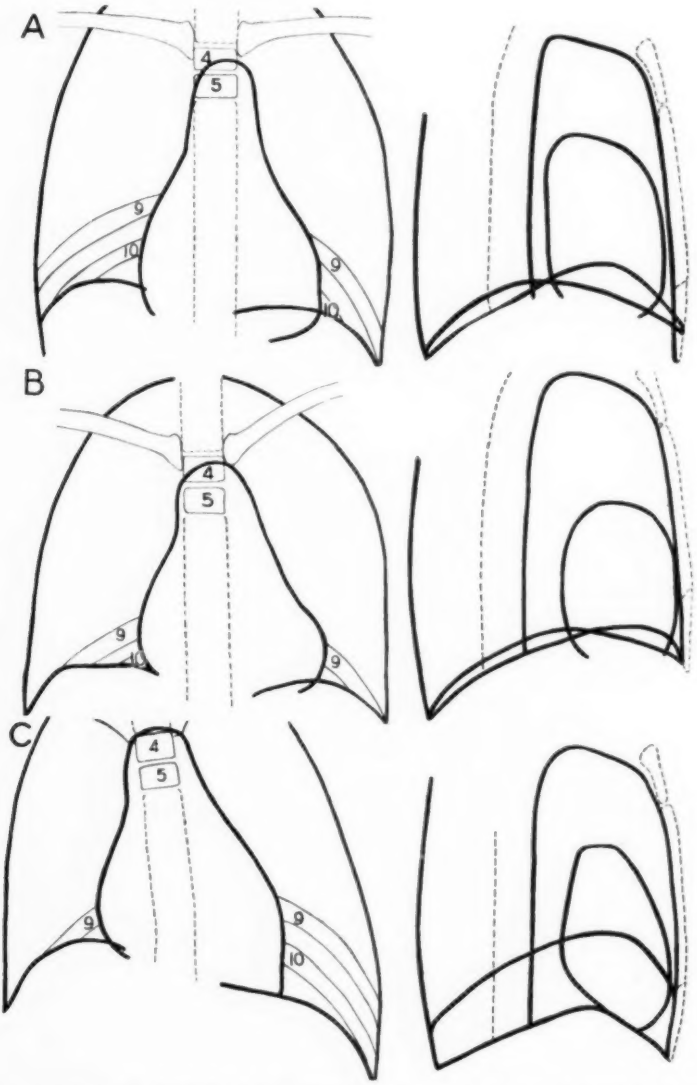


FIG. 1.—Tracings from 6-foot Roentgen ray plates of heart and chest of normal subject in different body postures. The anteroposterior views are on left; the lateral views on right of figure. Tracings *A*, taken with subject lying on back; *B*, subject sitting upright; *C*, subject lying on right side.

as a unit without rotation, and 5, alteration in the contour of the chest cavity.

The Roentgen ray plates also showed clearly that the right and left segments of the diaphragm as well as the anterior and posterior segments moved different amounts and sometimes even in different directions in different postures. Forward and lateral flexions of the vertebral column were also demonstrated in these plates.

The forces operating to bring these changes about are:

1. The action of gravity (*a*), pulling directly on the heart and rotating it around the 3 axes; (*b*), displacing the heart as a whole because the specific gravity of the heart is greater than that of the air-filled lung; (*c*), displacing the abdominal contents and consequently the segments of the diaphragm with which the heart is closely in contact.

2. The action of flexion and extension of the hip joint and the lumbar and thoracic vertebræ, the former varying the intraäbdominal pressure and so the position of the diaphragm, the latter causing alterations in the shape of the chest cavity.

The net result of these changes is that the electrical field of the body is altered. In part this is due to the rotation of the electrical field of the heart around the sagittal and the transverse axes. The electrical field of the heart on its epicardial surface is not affected by these changes, but the relation of the body to this electrical field is altered.

Another more important factor modifying the electrical field of the body is the alteration of the regions of the heart in contact with the anterior chest wall, with the diaphragm and with the posterior paravertebral muscle mass, which the work of Katz and Korey[4] has shown are good electrical conductors compared with the lungs which are poor electrical conductors. This latter change is in part due to displacement of the heart and in part to displacement of the lungs. As a result, different regions of the heart come in contact with these good conductors, and these good conductors come to occupy different parts of the wall of the chest cavity. The importance of this latter concept in explaining the electrocardiograms of pathologic hearts is being studied.

REFERENCES.

1. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the *Q-R-S* Complex of the Electrocardiogram, Arch. Int. Med., **36**, 614, 1925.

2. Nathanson, M. H.: Electrocardiographic Study of Movements of the Heart with Change of Posture, Proc. Soc. Exp. Biol. and Med., **28**, 766, 1931.

3. Katz, L. N., and Ackerman, W.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles, J. Clin. Invest., **11**, 1221, 1932.

4. Katz, L. N., and Korey, H.: Manner in which Electric Currents Generated by Heart are Conducted Away, Am. J. Physiol., **111**, 83, 1935.

PHYSIOLOGIC EFFECTS OF BENZEDRINE AND ITS RELATIONSHIP TO OTHER DRUGS AFFECTING THE AUTONOMIC NERVOUS SYSTEM.*

By Abraham Myerson, M.D.,

PROFESSOR OF NEUROLOGY, TUFTS COLLEGE MEDICAL SCHOOL; CLINICAL PROFESSOR OF PSYCHIATRY, HARVARD UNIVERSITY MEDICAL SCHOOL; VISITING PHYSICIAN, DEPARTMENT OF NERVOUS DISEASES, BOSTON CITY AND BETH ISRAEL HOSPITALS; DIRECTOR OF RESEARCH, BOSTON STATE HOSPITAL,

Julius Loman, M.D.,

JUNIOR VISITING NEUROLOGIST, BETH ISRAEL HOSPITAL; INSTRUCTOR IN NEUROLOGY, TUFTS COLLEGE MEDICAL SCHOOL; RESEARCH ASSOCIATE, BOSTON STATE HOSPITAL,

AND

William Dameshek, M.D.,

ASSOCIATE PHYSICIAN, BETH ISRAEL HOSPITAL; ASSISTANT PROFESSOR OF MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL; RESEARCH ASSOCIATE, BOSTON STATE HOSPITAL, MATTAPAN, MASS.

(From the Division of Psychiatric Research, Boston State Hospital.)

In the course of a group of studies on the drugs which affect the sympathetic and parasympathetic nervous systems, benzedrine was utilized as one of the sympathomimetic drugs. Its effects were so striking that a number of different types of observations were carried out. These are the subject of the paper which follows:

Benzedrine (phenylisopropylamine) is a synthetic preparation of the ephedrin and epinephrin group and belongs to the sympathomimetic class of drugs.[1] Most of the pharmacologic studies on benzedrine have been carried out on animals and have been mainly concerned with its effect on the blood pressure. Thus, Tainter,[1] Alles,[2] Hartung and Munch[3] have described the marked and prolonged pressor effect of the drug in animals. Similar observations have been made by Piness and Miller.[4] Clinically, benzedrine, like ephedrin, has been observed to have a marked decongesting effect on the mucous membrane of the nose, Eustachian tube and middle ear (Scarano,[5] Bertolet,[6] Byrne[7] and Wood[8]). In an important clinical paper, Prinzmetal and Bloomberg[9] have recently found that the drug is superior to ephedrin in the prevention of narcoleptic attacks.

This paper concerns a group of studies carried on for the purpose of adding pharmacologic and clinical data to the isolated observations hitherto reported. The other papers concern themselves, first, with the effect of benzedrine on the gastro-intestinal tract[10] and, second, with its effect on the mood and sense of wellbeing of groups of normal and mentally sick individuals.[11]

Material and Procedure. The subjects utilized in these experiments were mainly passive, submissive, unemotional cases of dementia præcox,

* Aided by grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.

who lay perfectly quiet throughout the entire procedure and whose general physical and physiologic states were known to us to be normal as a result of repeated and thorough studies. No preliminary anesthesia was used, thus eliminating an objectionable feature of the pharmacologic experiments done on animals. Eighteen patients, comprising 15 with dementia præcox, 2 with general paresis, and 1 with manic-depressive psychosis, were studied. These patients were brought to the laboratory without breakfast and allowed to rest for 15 to 30 minutes before the experiments were begun.

Benzedrine, given either orally, subcutaneously, or intramuscularly was administered either alone or in combination with other drugs, namely, sodium amytal, acetyl-Beta-methylcholin, and atropin. Its effects on the pulse, the blood pressure, the spinal fluid pressure, the basal metabolic rate, and the blood cellular constituents were studied. The effects of the drug on the gastro-intestinal tract and on the mood are the subjects of separate communications.

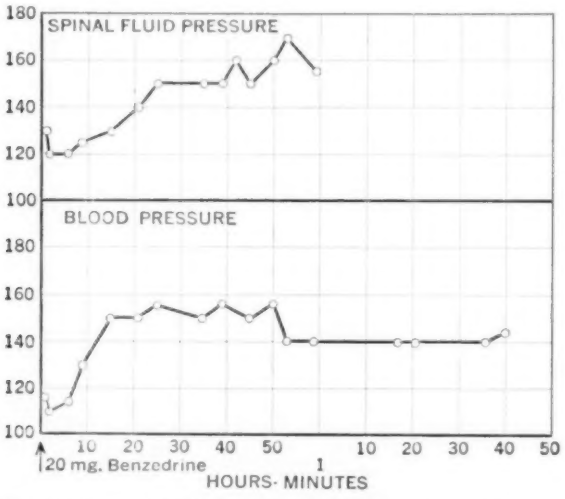


CHART I.—Effect of benzedrine (20 mg. s.c.) on the systemic arterial pressure and the cerebrospinal fluid pressure.

1. SUBCUTANEOUS ADMINISTRATION OF BENZEDRINE (Table 1, Chart I). *Blood Pressure.* In 18 cases benzedrine was administered subcutaneously in doses of 9 to 50 mg. In every instance but one a gradual rise in systolic pressure, varying from 10 to 64 mm. of mercury took place. The rise in diastolic pressure was not commensurate with the increase in systolic pressure. No precise relationship between the change in blood pressure and the dose administered could be determined, although the larger doses in general brought about the greater rise. The blood pressure reached its maximum in from 11 to 85 minutes and gradually returned to its original level in $1\frac{1}{2}$ to 7 or 8 hours.

Pulse. Simultaneously with the maximal increase in blood pressure, the pulse rate became diminished in 12 cases, remained un-

changed in 4 cases, and increased in 2 cases. The decrease in pulse rate varied from 4 to 25 beats per minute. Slight cardiac arrhythmia appeared in 4 cases; this was either of the sinus type or due to extrasystoles. During the rise in blood pressure, the pulse invariably became stronger.

TABLE 1.—EFFECTS ON THE BLOOD PRESSURE, PULSE AND SPINAL FLUID PRESSURE OF THE SUBCUTANEOUS ADMINISTRATION OF BENZEDRINE IN 18 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Dose, mg.	Control period.			Height of reaction.			Time.
			B.P.	Pulse.	S.F.P.	B.P.	Pulse.	S.F.P.	
E. B.	D.P.	48	100/60	84	150	134/70	60	175	53 min.
J. B.	D.P.	20	120/60	76	80	150/64	64	115	16 min.
E. Ba.	D.P.	29	126/80	68	150	152/80	56	180	32 min.
D. F.	D.P.	39	114/70	80	150	148/72	88	190	46 min.
A. F.	D.P.	9	84/50	80	95	108/70	80	130	29 min.
M. G.	D.P.	20	116/70	84	135	156/90	76	175	50 min.
J. G.	D.P.	20	100/58	72	105	134/82	60	140	33 min.
H. H.	D.P.	20	110/72	92	150	120/78	92	190	19 min.
J. McK.	M.D.	40	136/72	88	145	200/100	64	240	1 hr. 30 min.
H. B.	G.P.	21	112/72	100	...	130/76	88	...	24 min.
H. H.	D.P.	20	126/80	80	...	156/86	76	...	23 min.
J. McG.	D.P.	30	122/64	100	...	172/90	88	...	51 min.
H. P.	D.P.	30	100/62	80	160	140/80	80	190	1 hr. 17 min.
A. McN.	D.P.	20	100/68	92	115	124/76	92	140	38 min.
F. H.	D.P.	40	130/68	84	125	160/86	64	155	
J. M.	G.P.	30	138/86	100	175	172/90	72	210	1 hr. 45 min.
J. R.	D.P.	40	130/80	108	...	126/70	120	...	40 min.
J. M.	G.P.	30	138/90	92	...	152/90	88	...	53 min.

D.P. = dementia præcox; G.P. = general paresis; M.D. = manic-depressive psychosis; S.F.P. = spinal fluid pressure in mm. of water.

TABLE 2.—EFFECT ON THE BLOOD PRESSURE AND PULSE OF THE ORAL ADMINISTRATION OF BENZEDRINE IN 14 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Initial B.P.	Initial pulse.	B.P. at height.	Time.	Pulse at height.
J. C.	D.P.	126/70	80	160/82	46 min.	64
J. McG.	D.P.	126/70	92	160/80	1 hr. 20 min.	92
A. M.	D.P.	116/70	88	142/90	1 hr. 2 min.	90
J. B.	D.P.	126/70	100	134/80	49 min.	68
H. H.	D.P.	114/80	80	158/80	39 min.	84
F. H.	D.P.	126/76	80	150/40	40 min.	112
E. B.	D.P.	132/80	64	190/110	26 min.	52
A. F.	D.P.	100/66	72	122/70	2 hr.	64
H. B.	G.P.	120/78	84	148/82	52 min.	72
J. G.	D.P.	104/70	88	150/90	43 min.	84
C. P.	D.P.	130/96	84	164/92	1 hr. 40 min.	64
E. B.	D.P.	124/70	76	150/86	2 hr. 25 min.	56
J. P.	D.P.	120/70	96	140/80	1 hr. 12 min.	72
J. G.	D.P.	104/60	56	172/90	47 min.	52

Spinal Fluid Pressure. A uniform rise in the spinal fluid pressure was noted in the 14 cases in which it was followed. In 13 cases the increase varied from 25 to 40 mm. of water. In the other case it

rose 95 mm. This was in the subject who manifested the greatest rise in blood pressure. The maximal spinal fluid pressure occurred at about the time the blood pressure was at its height.

2. Oral Administration of Benzedrine (Table 2). Fourteen of the subjects were given 40 mg. of benzedrine by mouth and the blood pressure and pulse observed. There was a rise of blood pressure in every case, varying from 8 to 68 mm. of mercury. These figures are roughly similar to those observed in the same group of subjects when the drug was administered subcutaneously. With oral administration, however, in most instances the blood pressure reached its height more slowly, that is, in 20 minutes to 2 hours and 25 minutes. In the majority of instances the pulse rate diminished

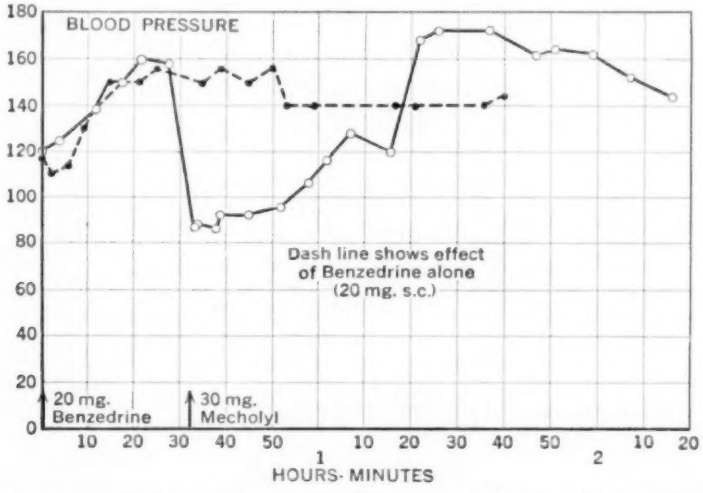


Chart II.—Effect on the blood pressure of benzedrine (20 mg. s.c.) alone and when followed by mecholyl (30 mg. s.c.). It is seen that with subsidence of the mecholyl effect, the benzedrine reaction continued unabated, the blood pressure returning to an even higher level than originally.

3. The Combined Effect of Benzedrine and Acetyl-Beta-methylcholin (Mecholyl). Seven cases of dementia præcox were first given benzedrine subcutaneously in doses varying from 20 to 50 mg. The rise in blood pressure varied from 20 to 40 mm. of mercury and there was a drop in pulse rate varying from 2 to 16 beats per minute. When the blood pressure had reached its height, mecholyl, an active parasympathetic stimulant, was administered subcutaneously in dosage of 20 to 30 mg. Within a few minutes following this injection, the blood pressure dropped sharply 36 to 96 mm. of mercury systolic and 20 to 54 mm. diastolic. Coincidentally with the marked fall in blood pressure there was a sudden rise in pulse rate in 6 cases, varying from 40 to 62 beats per minute.

In the other case there was a slowing of 12 beats per minute. The usual effects of mecholyl, namely, flushing of the face, neck, chest, and back, lacrimation, salivation, rhinorrhea, and perspiration

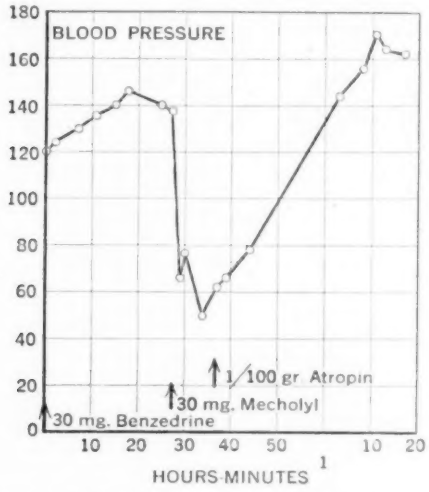


CHART III.—Effect on the blood pressure of benzedrine (30 mg. s.c.) followed by mecholyl (30 mg. s.c.). The great fall in blood pressure produced by mecholyl was quickly counteracted by atropin (gr. 1/100 s.c.), the blood pressure returning to an even higher level than that obtaining during the benzedrine reaction.

TABLE 3.—EFFECT ON THE BLOOD PRESSURE AND PULSE OF THE ADMINISTRATION OF BENZEDRINE (S.C.) AND MECHOLYL (S.C.) ON 7 DEMENTIA PRÆCOX SUBJECTS.

Case.	Diagnosis.	Control period.		Benzedrine.				Mecholyl.				Reaction at end of experiment.		
				Height of reaction.				Height of reaction.						
		B.P.	Pulse.	Dose (mg.).	B.P.	Time (min.).	Pulse.	Dose (mg.).	B.P.	Time (min.).*	Pulse.	B.P.	Time.†	Pulse.
M. G.	D.P.	120/80	80	20	160/100	28	68	30	86/54	6	112	172/100	1 hr. 37 min.	60
H. P.	D.P.	120/80	96	30	146/90	18	92	30	50/36	7	80	170/120	1 hr. 13 min.	112
J. P.	D.P.	142/80	84	40	170/100	47	80	20	134/80	1	120	152/80	1 hr. 41 min.	84
F. H.	D.P.	130/70	92	20	150/90	46	80	20	100/70	2	126	150/70	2 hr. 14 min.	68
J. McG.	D.P.	120/70	108	30	154/86	20	96	30	84/46	3	140	158/88	1 hr. 15 min.	68
J. B.	D.P.	126/68	84	40	156/80	19	68	30	94/60	1	112	156/80	1 hr. 17 min.	54
J. G.	D.P.	118/80	72	50	140/90	21	70	30	60/40	3	132	168/90	2 hr. 33 min.	48

* Time from the administration of the mecholyl.
† Time from the beginning of the experiment.

occurred in varying degrees and differed in no essential manner from those reported by other experimenters and observed by us in another group of subjects. With the subsidence of the mecholyl

effects, which occurred within 10 to 30 minutes, there was a steady rise in blood pressure which finally, with but one exception, reached a height at least as great as that which had obtained at the height of the benzedrine reaction. The pulse was now slower in 5 of the cases than during the height of the benzedrine reaction. (Table 3, Charts II and III.)

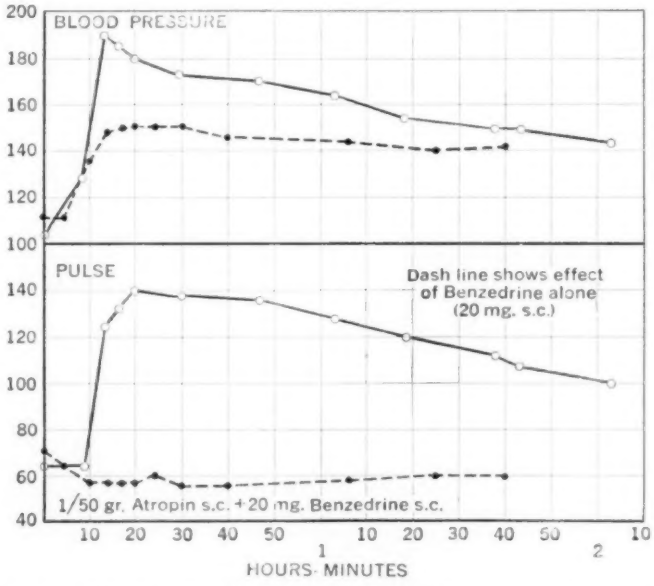


CHART IV.—Effect on the blood pressure of benzedrine alone and of benzedrine combined with atropin in the same subject a week later. It is seen that the combined effect of benzedrine and atropin produced a greater rise in blood pressure than that by benzedrine alone. This was probably due to an enhanced sympathetic effect when the parasympathetic system was paralyzed.

4. THE COMBINED EFFECT OF BENZEDRINE AND ATROPIN. Studies of the effect of atropin sulphate when given either together with benzedrine or just prior to it are now in progress, and the results cannot be given in detail. In 4 of 11 cases the rise in blood pressure was great, exceeding by far the rise obtained in the same patients when given benzedrine alone on previous occasions. (Chart IV.)

5. THE COMBINED EFFECT OF BENZEDRINE AND SODIUM AMYTAL.

A. Benzedrine followed by sodium amytal (Table 4, Chart V).

Benzedrine (20 to 50 mg.) was administered subcutaneously to 7 subjects. When the blood pressure had reached its maximum level, sodium amytal (.5 to .7 gm.) was injected intravenously. A sudden drop in pressure occurred reaching its lowest level soon after the completion of the injection of sodium amytal. The fall in systolic blood pressure varied from 4 to 40 mm. of mercury. All of the subjects fell asleep during the administration of the amytal. In 5

patients who were soundly asleep the blood pressure again rose and reached a level higher than that obtaining during the control period. In the other 2 cases the blood pressure was 8 to 10 mm. lower during the height of the amytal narcosis than during the control period. Although the depth of the narcosis did not appear to be affected, its duration, as compared with that occurring in a previously studied group of patients, appeared to be definitely shortened.[12] During the amytal narcosis, the pulse again increased in 5 cases and diminished slightly in the other 2.

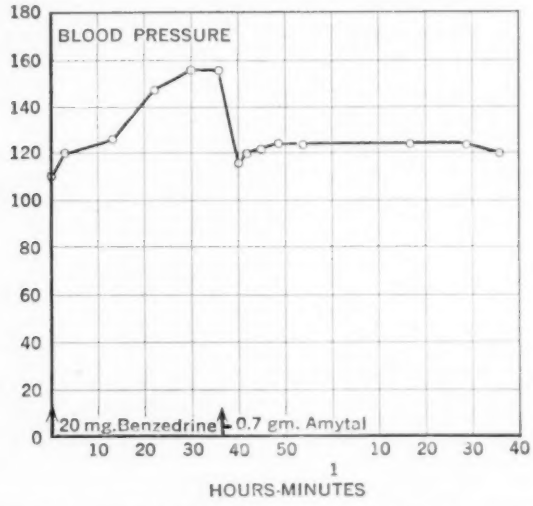


CHART V.—Effect on the blood pressure of benzedrine (20 mg. s.c.) followed by sodium amytal (0.7 gm. i.v.). The sodium amytal acted as usual to lower the blood pressure after a rise due to benzedrine. There was no fall in blood pressure below the original level.

If the reaction of the blood pressure to the injection of both benzedrine and sodium amytal is compared with that occurring to amytal alone, it will be observed that in the latter group the blood pressure returns to its original level in a longer period of time (Table 5). In other words, it appears that the effect of benzedrine, when given together with the amytal, was to shorten the blood pressure lowering period.

The spinal fluid pressure was observed in 5 of the above 7 cases (Table 4). In 2 cases it fell slightly during the amytal narcosis and at the end of the experiment returned to the original level. In the other 3 cases the spinal fluid pressure varied but slightly during the entire experiment.

B. Sodium Amytal Followed by Benzedrine (Table 6, Chart VI). Seven subjects received .5 to .8 gm. sodium amytal intravenously. At the completion of the injections, the fall in systolic blood pressure

TABLE 5.—EFFECT ON THE BLOOD PRESSURE, PULSE AND CEREBROSPINAL FLUID PRESSURE OF THE ADMINISTRATION OF BENZEDRINE (S.C.) FOLLOWED BY SODIUM AMYTAL (I.V.) ON 7 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Control period.			Benzedrine, height of reaction.					Sodium amytal, height of reaction.					Reaction at end of experiment.			
		B.P.	Pulse.	S.F.P.	Dose, s.c. (mg.).	B.P.	Time* (min.).	Pulse.	S.F.P.	Dose i.v. (gm.).	B.P.	Time† (min.).	Pulse.	S.F.P.	B.P.	Pulse.	Time.‡	S.F.P.
J. M.	G.P.	136/84	84	...	40	158/100	50	128	...	0.7	146/100	5	120	...	168/100	128	1 hr. 10 min.	
M. G.	D.P.	114/80	84	120	20	160/96	19	76	120	0.5	130/84	55	72	110	140/80	70	2 hr. 42 min.	140
E. Ba.	D.P.	110/70	72	80	20	156/96	30	56	80	0.7	116/80	4	72	65	120/88	56	1 hr. 35 min.	105
E. B.	D.P.	104/66	88	140	40	130/80	44	85	160	0.6	114/78	5	112	150	124/80	100	1 hr. 50 min.	145
D. F.	D.P.	106/60	76	130	30	138/80	40	68	125	0.7	134/82	19	76	140	124/76	72	1 hr. 44 min.	130
F. H.	D.P.	130/68	84	125	40	160/86	49	64	150	0.6	120/70	3	84	135	148/80	60	2 hr.	125
H. P.	D.P.	126/84	108	...	50	148/82	50	84	...	0.7	118/86	6	120	...	144/90	100	2 hr. 30 min.	...

* Time from benzedrine injection. † Time from beginning of amytal injection. ‡ Time from beginning of experiment.

TABLE 6.—EFFECT ON THE BLOOD PRESSURE, PULSE AND CEREBROSPINAL FLUID PRESSURE OF THE ADMINISTRATION OF SODIUM AMYTAL (I.V.) FOLLOWED BY BENZEDRINE (S.C.) ON 7 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Control period.			Sodium amytal, height of reaction.					Benzedrine, height of reaction.					Reaction at end of experiment.			
		B.P.	Pulse.	S.F.P.	Dose, i.v. (gm.)	B.P.	Pulse.	S.F.P.	Time* (min.).	Dose, s.c. (mg.).	B.P.	Pulse.	S.F.P.	Time† (min.).	B.P.	Pulse	Time.‡	S.F.P.
H. H.	D.P.	130/90	92	165	0.7	90/70	96	190	17	20	136/90	96	150	20	128/86	92	1 hr. 12 min.	150
H. B.	G.P.	110/70	104	180	0.7	68/50	100	150	4	30	90/50	80	160	38	88/54	84	1hr.	120
J. B.	D.P.	114/60	92	90	0.7	78/56	84	100	19	20	124/70	76	100	33	106/74	80	1 hr. 40 min.	125
J. G.	D.P.	102/60	84	25	0.6–0.7	68/46	64	25	3	20	130/76	52	100	50	116/80	50	1 hr. 25 min.	130
E. Ba.	D.P.	128/90	72	...	0.7	98/66	68	...	4	40	188/114	52	...	45	168/106	56	2 hr. 40 min.	
J. McG.	D.P.	132/70	100	...	0.8	110/68	88	...	5	30	142/96	84	...	28	134/88	88	2 hr. 19 min.	
H. G.	D.P.	128/82	72	...	0.6	88/68	88	...	4	30	160/106	68	...	43	148/98	68	2 hr. 7 min.	

* Time from beginning of amytal injection. † Time from beginning of benzedrine injection. ‡ Time from beginning of experiment.

varied from 16 to 42 mm. of mercury. Benzedrine in doses varying from 20 to 40 mg. was now administered subcutaneously. Within 5 to 10 minutes following this injection, the blood pressure in 6 cases began to rise, reaching a level at least as high as the original one within 21 to 41 minutes. In the other case the blood pressure slowly rose after an original drop from the injection of amytal, but did not reach the original level. Although the depth of narcosis did not appear to be affected by the benzedrine, its duration seemed to be definitely shortened as compared with a group in which amytal alone had been given.

TABLE 5.—EFFECT OF THE ADMINISTRATION OF SODIUM AMYTAL (I.V.) ON 12 SUBJECTS WITH MENTAL DISEASE. COMPARE THE BLOOD PRESSURE RESPONSE TO THAT SHOWN IN TABLES 4 AND 6 (COMBINED EFFECT OF SODIUM AMYTAL AND BENZEDRINE).

			Control period.		At height.			At end.		
Case.	Diagnosis.	Dose, I.V. (gm.).	B.P.	Pulse.	Time.	B.P.	Pulse.	Time	B.P.	Pulse.
H. H.	D.P.	1.0	106/64	96	12 min.	90/70	96	4 hr. 13 min.	96/64	76
H. B.	G.P.	0.3	102/66	74	29 "	78/44	80	1 hr.	90/64	74
C. P.	D.P.	0.3	158/88	60	10 "	110/60	58	1 hr. 7 min.	110/60	58
J. N.	M.D.	0.25	110/44	72	41 "	88/38	60	1 hr. 9 min.	102/40	56
J. B.	D.P.	0.25	110/50	60	30 "	90/40	60	1 hr.	98/50	72
E. B.	D.P.	0.2	130/60	80	30 "	108/68	60	1 hr.	114/64	60
C. P.	D.P.	0.2	140/82	66	40 "	120/80	60	1 hr.	132/76	60
G. D.	G.P.	1.0	144/64	90	47 "	90/54	90	1 hr. 7 min.	92/56	90
G. T.	G.P.	0.8	120/60	84	21 "	94/50	76	1 hr. 11 min.	96/56	72
C. Pe.	D.P.	1.0	122/70	92	33 "	82/	96	1 hr. 12 min.	98/60	78
H. P.	D.P.	1.0	100/56	72	16 "	84/50	72	1 hr.	98/56	66
J. B.	D.P.	1.0	124/64	..	1 hr. 1 min.	80/66	..	1 hr. 26 min.	98/60	

The pulse rate became diminished in 5 cases. In the other 2 cases a slight rise occurred following administration of sodium amytal. During the benzedrine reaction the pulse dropped to a still lower level in 6 of the cases. At the end of the experiment the pulse was slower in all but one of the cases than it was during the control period. The spinal fluid pressure showed no consistent variations.

6. OTHER STUDIES. *A. Hematology.* Studies of the hemoglobin, red cell count, white cell count, and differential count of the white cells were made in a group of 15 patients before and after administration of benzedrine. The following techniques were used: Hemoglobin was determined by the Sahli method, calibrated against the Van Slyke-Neill oxygen capacity method so that 100% equal 15.5 gm. of hemoglobin per 100 cc. In addition, the hemoglobin concentration was determined in each individual by the oxygen capacity method at the beginning of the experiment, once during its course,

and once at the end of the experiment. The erythrocyte and leukocyte counts were performed with standardized pipettes and hemacytometers, the same apparatus being utilized throughout the experiments. The hematocrit determinations were made with heparinized blood utilizing the hematocrit tubes of Wintrobe, the centrifuge speed being 3000 revolutions per minute, complete packing occurring in 30 minutes. The effects of the drug were quite variable, although in several instances striking. In 4 of the cases studied the red cell count rose 1.5 to 3 millions per c.mm. within 2 hours after administration of the drug without, however, any definite rise in hemoglobin. In 7 other cases the red cell count rose about

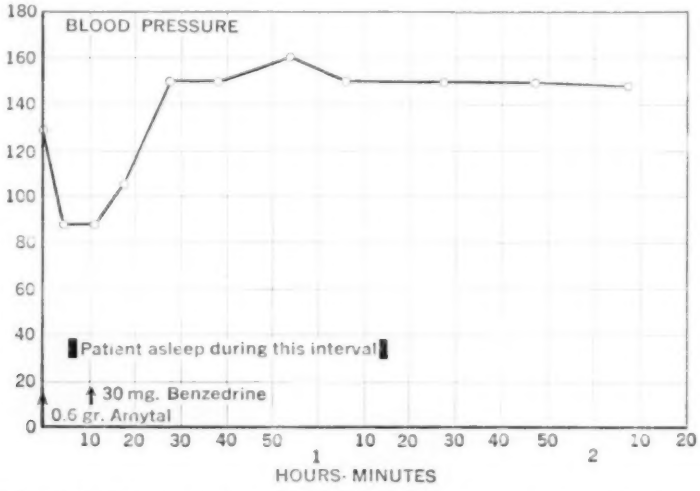


CHART VI.—Effect of sodium amytal (0.6 gm. i.v.) followed by benzedrine (30 mg. s.c.). The fall in blood pressure caused by the sodium amytal was soon counteracted by the benzedrine so that the blood pressure rose even higher than its original level. Although the depth of the narcosis is not disturbed by the benzedrine, the duration of the anesthesia is definitely shortened.

1 million. The leukocyte count became doubled, tripled, and even quadrupled in 4 of the cases; this was associated with a striking polymorphonuclear leukocytosis, although there was no increase in immature cells. In the other cases there was slight or moderate increase in white cells with an almost invariable increase in neutrophils. In 2 cases in which venous blood cell counts were compared with those of the peripheral blood, there was close agreement indicating that the observed findings were not due merely to changes in the peripheral circulation. There was no definite observed correlation between the extent of the blood pressure rise and that of the blood cellular constituents, nor could we predict in which patient a striking rise would take place (Chart VII).

Two subjects, who had shown a rather marked rise in red cell count, were given daily injections of benzedrine. In both, a steplike progression in red cell count occurred, so that at the end of 4 days

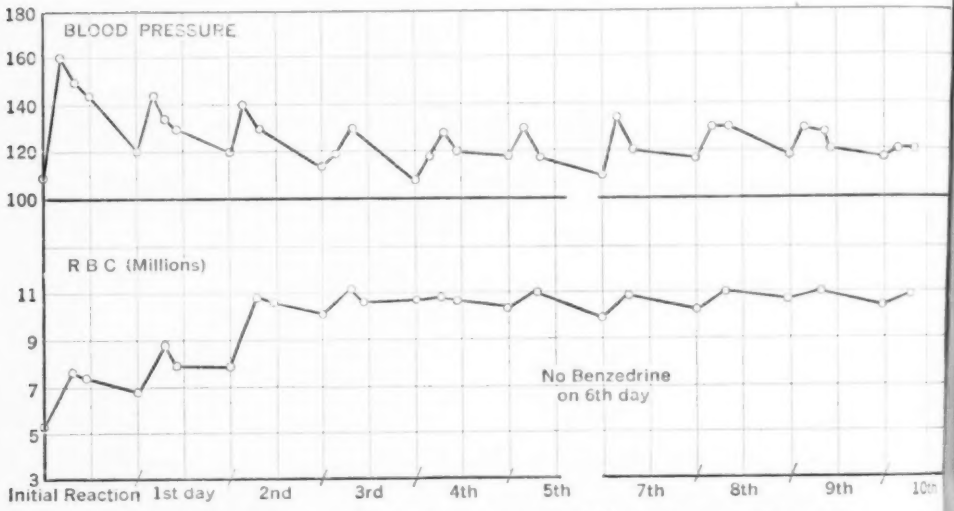


CHART VII.—Effect on the blood pressure and red blood cell count of benzedrine (40 mg. s.c.) given daily. The red count rose in steplike progression from a normal count of 5.3 millions to 10.9 millions in 4 days, remaining at about that level for 6 more days. The blood pressure showed less and less reaction until on the 10th day no rise occurred.

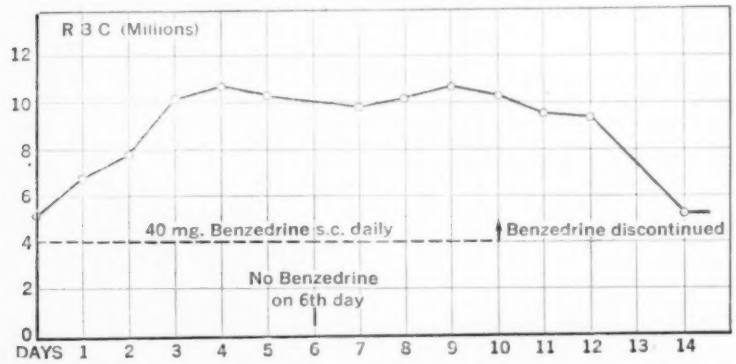


CHART VIII.—Same subject as in Chart VII. The benzedrine was discontinued on the 10th day and the red blood count gradually fell, reaching its original level on the 14th day.

the erythrocytes numbered respectively 9.3 and 10.9 millions per c.mm. There was only slight corresponding increase in hemoglobin and volume of packed red cells, however, indicating possibly that a number of very thin, red cells were present in the circulation. Further

studies of this interesting phenomenon are being carried out and will be the subject of another report (Chart VIII).

B. Effects on Metabolism and Sugar Content of Blood. The basal metabolic rate was studied before and during benzedrine. No significant changes were discovered, despite the fact that patients who could give an adequate account of their reactions stated that they felt somewhat flushed after taking the drug. No change occurred in the carbohydrate metabolism as indicated by the lack of rise in the blood sugar when the drug was given.

C. A special study of the effect of benzedrine on the *tonus and motility of the gastro-intestinal tract* is at present in progress. It suffices to say at this point that benzedrine exercises a greatly relaxing effect upon spasticity. An account of these phenomena appears in another paper.

D. In another paper a clinical account is given of the effect of benzedrine upon *fatigue and depression* in certain patients seen in hospital and private practice. At this point it will suffice to say that in the normal individual benzedrine exercises a striking effect in dissipating the sense of fatigue together with the mild depressed feeling which is frequently present. The effects of the drug are noted within a few minutes after oral administration and persist for several hours. If taken within a few hours of bedtime, the effect is to banish sleep entirely. This is quite in line with the observations made by Prinzmetal and Bloomberg in narcolepsy.

Discussion. The effect of benzedrine on the blood pressure of subjects with mental disease appears to be similar to that reported by other observers working on animals and man. There was no apparent change in the mental reactions of the subjects observed, although it was difficult or impossible in these patients to elicit any subjective manifestations of the drug. The effects of the drug on the symptoms of fatigue and depression in various clinical studies are discussed in an accompanying article.

That benzedrine produces a central stimulating effect is indicated by its efficacy in narcolepsy, its ability to arouse animals from barbital anesthesia, and by the fact that it shortens the period of sodium amytal narcosis, as indicated in the present study.

The rise in cerebrospinal fluid pressure in most cases may indicate a slight increase in cerebral venous pressure or a slight cerebral vasodilatation, although there is, at the same time, a general vasoconstrictor effect of the drug. In a few cases the failure of the cerebrospinal fluid pressure to rise, even in the presence of a moderate rise in arterial pressure points to an unchanged diameter of the cerebral vessels. A rise in arterial pressure, occurring either with slight or no change in cerebral vessel diameter indicates, as pointed out by Gibbs and his co-workers[13] and by Loman and Myerson[14, 15] an increase in cerebral blood flow. Benzedrine is thus similar to adrenalin in its vascular effects, although the latter drug acts more rapidly and

actively. It is unlikely, however, that an increase in cerebral blood flow explains the cerebral stimulating effect of the drug. The central effect of benzedrine appears to be due to some direct chemical action on the brain.

The reactions following the combined administration of benzedrine and mecholyl or atropin allow one to study the effects of simultaneous stimulation or depression of the sympathetic and parasympathetic systems. It is observed that the parasympathetic stimulating effects of mecholyl do not counteract or balance the sympathetic effects of benzedrine, but that the two drugs result in sharply distinct individual reactions. Thus, all the usual effects of mecholyl occur and have about the same duration as when this drug is administered alone. When the mecholyl reaction is spent, the effect of the benzedrine continues undisturbed. This is in contrast to the combined effect of epinephrin and mecholyl, since the effects of epinephrin are short-lived, whereas the effects of benzedrine are present for hours.

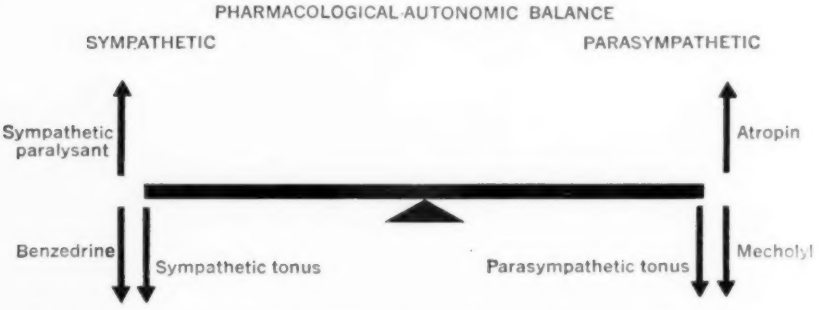


FIG. 1.—Schema of antagonistic activity of sympathetic and parasympathetic systems conceived as forces acting at opposite ends of a balanced lever.

Paralysis of the parasympathetic system by the use of atropin apparently enhances the action of the sympathetic stimulant, benzedrine. This suggests a constantly active system of "checks and balances" existing between the sympathetic and parasympathetic systems (Fig. 1). When the sympathetic is stimulated, as by benzedrine, a complete effect may not be obtained because of the continued activity of the parasympathetic. When, however, the latter system is paralyzed, as by atropin, the complete effect may occur. The remarkable effects of these various drugs on the circulation suggest that by methods of neuro-pharmacologic equilibration, it might be possible to exert dramatic clinical effects with their proper use.

A similar qualitative effect is seen when sodium amytal is given at the height of the benzedrine reaction. Although a drop in blood pressure follows the administration of sodium amytal, the blood pressure returns to its original or a higher level under the effect of

the benzedrine and in a much shorter time than it would if the former drug were given alone. These experiments further show definitely that the associated drop in blood pressure is not essential to the production of sleep in amytal narcosis, since the patients continued to sleep even when the blood pressure was rising under the influence of benzedrine, although the period of narcosis was shorter. Moreover, small doses of benzedrine, which almost completely destroy the ability to sleep, do not create any change in blood pressure. It would thus seem certain that sleep is not fundamentally dependent upon either a lowered or an increased blood pressure.

The striking effects on the cellular constituents of the blood are probably due to squeezing out of cells, chiefly red cells, from various storage depots. The well known constricting effect of adrenalin on the spleen is probably simulated in this instance by benzedrine. It is also likely that cells from other organs, such as the bone marrow or the lungs, are squeezed out by effects of the vasoconstrictor action of the drug and thus appear in the circulation. The absence of immature forms of either white or red cells suggests that the increase in counts is a mechanical one and not due to stimulation of the blood-forming organs.

Summary and Conclusions. Benzedrine, a sympathomimetic drug, was studied in a group of patients with mental disease, its effect on the pulse, blood pressure, spinal fluid pressure, mental state, basal metabolism, and blood cellular constituents being noted. Its actions when used in combination with acetyl-beta-methylcholin (mecholyl, a parasympathetic stimulant), atropin and sodium amytal were observed.

Benzedrine has a striking and prolonged effect in raising the blood pressure, together with a less marked effect on the spinal fluid pressure. Its effects in raising the red cell and white cell counts are often great, the erythrocyte count rising 1 to 3 millions per c.mm. and the leukocyte count often being doubled or even tripled. No effects on the basal metabolic rate or blood sugar were noted.

When used with mecholyl, the blood pressure lowering effect of the latter drug was at first apparent, followed by an increased blood pressure when the effects of mecholyl became diminished. When used with atropin, the rise in blood pressure was often extreme. With amytal, the period of narcosis was shortened and the blood pressure lowering effect of this drug was diminished.

As brought out in these and associated studies, benzedrine has a central stimulating effect. Its effects are, in general, those of a sympathetic stimulant, the reaction being a prolonged one of several hours' duration. Its effects on the blood cellular constituents are probably due to vasoconstriction of the spleen and other reservoirs of blood cells resulting in an increased number of cells in the peripheral blood.

The effects of the combined administration of benzedrine with

mecholyl, atropin, and sodium amytal are exceedingly interesting and suggest that it may be possible to equilibrate sympathetic and parasympathetic drugs against each other, and thus obtain enhanced effects.

The central, vascular, and smooth muscle effects of benzedrine suggest its practical use in various clinical conditions. Its ability to arouse narcoleptics has already been mentioned. Its stimulating effect in psychoneuroses and in mental and fatigue states is important and is elaborated upon in an accompanying article. Because of its ability to raise and maintain arterial pressure over a period of several hours, its use in counteracting an expected fall in blood pressure, as for example in anesthesia, or in raising the blood pressure in conditions of peripheral circulatory failure, as in shock, pneumonia, etc., is suggested. It may be of value as well in the ill-defined condition known as primary or postural hypotension. Its use in diminishing increased tonus of organs made up in great part of smooth muscle—such as the gastro-intestinal tract, the ureter, and gall bladder—seems to be definitely indicated. The use of benzedrine in individuals known to have hypertension or severe vascular or cardiac disease is probably contra-indicated.

REFERENCES.

1. Tainter, M. L.: Comparative Actions of Sympathomimetic Compounds: Phenyl and Substituted Phenyl Derivatives, Non-phenylic Ring Compounds, and Aliphatic Amines, Arch. Internat. de pharmacod., **46**, 192, 1933.

2. Alles, G. A.: The Comparative Physiological Action of dl-Beta-phenylisopropylamine. I. Pressor Effect and Toxicity, J. Pharm. and Exp. Therap., **47**, 339, 1933.

3. Hartung, W. H., and Munch, J. C.: Amino Alcohols. VI. The Preparation and Pharmacodynamic Activity of 4 Isomeric Phenylpropylamines, J. Am. Chem. Soc., **53**, 1875, 1931.

4. Piness, G., Miller, H., and Alles, G. A.: Clinical Observations on Phenylaminoethanol Sulphate, J. Am. Med. Assn., **94**, 790, 1930.

5. Scarano, J. A.: Rapidity of Shrinkage and Immediate and Secondary Reactions Following Local Applications of Ephedrine and Benzedrine, Med. Rec., **140**, 602, 1934.

6. Bertolet, J. A.: Benzyl Methyl Carbinamine Carbonate, Med. J. and Rec., **136**, 75, 1932.

7. Byrne, H. V.: The Use of Benzyl-methyl-carbinamine-carbonate in the Treatment of Rhinitis, New England J. Med., **209**, 1048, 1933.

8. Wood, E. L.: A New Drug for Treatment of the Eustachian Tube and Middle Ear, Arch. Otolaryngol., **21**, 588, 1935.

9. Prinzmetal, M., and Bloomberg, W.: The Use of Benzedrine for the Treatment of Narcolepsy, J. Am. Med. Assn., **105**, 2051, 1935.

10. Myerson, A., and Ritvo, M.: Benzedrine Sulphate and Its Value in Spasm of the Gastro-intestinal Tract, J. Am. Med. Assn., **107**, 24, 1936.

11. Myerson, A.: Effect of Benzedrine Sulphate on Mood and Fatigue in Normal and Neurotic Persons, Arch. Neurol. and Psychiat. (in press).

12. Dameshek, W., Myerson, A. and Loman, J.: The Effects of Sodium Amytal on the Metabolism, Am. J. Psychiat., **91**, 1, 113, 1934.

13. Gibbs, F. A., Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow in Man as Influenced by Adrenalin, Caffeine, Amyl Nitrite and Histamine, Am. Heart J., **10**, 916, 1935.

14. Loman, J., and Myerson, A.: Studies in the Dynamics of the Human Craniovertebral Cavity, Am. J. Psychiat., **92**, 791, 1936.

15. Loman, J., and Myerson, A.: The Action of Certain Drugs on the Cerebrospinal Fluid and on the Internal Jugular Venous and Systemic Arterial Pressures of Man, Arch. Neurol. and Psychiat., **27**, 1226, 1932.

BOOK REVIEWS AND NOTICES.

DISEASES OF THE LIVER, GALL BLADDER, DUCTS AND PANCREAS. Their Diagnosis and Treatment. By SAMUEL WEISS, M.D., F.A.C.P., Clinical Professor of Gastroenterology, New York Polyclinic Medical School and Hospital; Attending Gastroenterologist, Jewish Memorial and Beth David Hospitals, New York, etc. Chapter on Surgery by J. Prescott Grant, M.D., F.A.C.S., M.R.C.S., Professor of Surgery, New York Polyclinic Medical School and Hospital; Attending Surgeon, City Hospital; Director of Surgery, Midtown Hospital. Chapter on Roentgenology by A. Judson Quimby, M.D., F.A.C.R., Professor of Roentgenology, New York Polyclinic Medical School and Hospital; Visiting Roentgenologist, Broad Street Hospital. Pp. 1099; 358 illustrations, 6 color plates, and 21 tables. New York: Paul B. Hoeber, Inc., 1935. Price, $10.00.

IN covering his subject the author has attempted to include an enormous amount of material from the literature (over a hundred pages are devoted to references and an index of personal names). One, however, gets the impression that much of this material has been not too well assimilated and the reader finds the going rather heavy. If the author had condensed his manuscript by one-fourth and had been somewhat more critical of the balance, he would have produced a more readable and a more authoritative text. Aside from these shortcomings, the book has much to recommend it. The historical notations are interesting. The discussion of examination of liver and gall bladder, the sections on pathology and particularly the illustrations, are well done.

R. K.

THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE PERIPHERAL ARTERIES. By SAUL S. SAMUELS, A.M., M.D., Chief of the Clinic for Peripheral Arterial Diseases, Fourth Division Bellevue Hospital, New York; Chief of the Department of Arterial Diseases, Stuyvesant Polyclinic Hospital, New York, etc. Pp. 260; 51 illustrations. New York: Oxford University Press, 1936. Price, $3.50.

THIS monograph is first of all a plea for the conservative management of thromboangiitis obliterans, to which disease almost two-thirds of the book is devoted. The demonstration of the very frequent good results of such therapy, reflecting a large experience with Buerger's disease, give the book its chief value.

The author is equally intent in his partiality toward the intravenous hypertonic saline treatment for obliterative diseases of the peripheral vessels. Though recognizing the need for all available proven methods that promote collateral circulation, he dismisses, with evident lack of understanding, such methods as intravenous typhoid antigen injections, alternating suction and pressure, and sympathetic ganglionectomy, methods which other competent judges regard as useful. A statement frankly admitting insufficient experience with such procedures for sound judgment, or that they had failed after thorough trial in his hands, would seem more in keeping with the expressed purpose of the book.

Likewise the vasospastic disorders and their differentiation from occlusive disease, deserve more detailed consideration than they receive in this treatise intended to cover diseases of the peripheral arteries.

The book contains many sensible and extremely valuable diagnostic and therapeutic suggestions tersely stated. In this respect and in its well documented case for conservatism it is of real value to the practitioner.

L. H.

TIME OF OVULATION IN WOMEN. A Study of the Fertile Period in the Menstrual Cycle. By CARL G. HARTMAN, Department of Embryology, Carnegie Institution of Washington, John Hopkins Medical School, Baltimore, etc. Pp. 226; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, $3.00.

THIS small volume gives a thorough analysis of the present knowledge of human ovulation with particular reference to the Ogino-Knauss theory of a "safe" period. The clear and concise explanations will be easily grasped by the more intelligent laity, although the book is not primarily offered to them. The text discusses the physiology of the germ cells, the sex cycle, the menstrual cycle and its variations. The time of ovulation is discussed especially in its physiologic and hormonal relationships.

Ovulation as observed in the Carnegie Institute monkey colony is compared with ovulation in the human. He brings out the practical application of the present understanding of ovulation in the human to the correction of apparent sterility. The large number of well executed graphs should lend greatly to a quick and clear understanding of the text by a lay reader. For physicians this very instructive review will provide a means for easy explanation of the biologic mystery of conception to patients.

P. W.

FOUNDATIONS OF SHORT WAVE THERAPY. Physics-Technics-Indications. Physics and Technics by WOLFANG HOLZER, DR. MED., Assistant in the Physiologic Institute of the University of Vienna; Medical Applications by EUGEN WEISSENBERG, DR. MED.; Medical Superintendent of the Short Wave Section of the University Clinic for Nervous and Mental Diseases in Vienna. Translated by JUSTINA WILSON, F.R.C.P. (EDIN.,) D.M.R.E. (CANTAB.), and CHARLES M. DOWSE, B.SC. ENG. (LOND.,) A.M.I.E.E. Pp. 228; 53 illustrations and 10 tables. London: Hutchinson & Co., Ltd., 1936. Price, 12/6.

THE technical section of the book illustrates an attempt at treating a somewhat advanced subject in an elementary fashion. This led to partial inaccuracies. The terminology was not always good but this may be a difficulty in translation.

In regard to the mechanism of action, it is the feeling of some authors that it is unlikely that there is any specific action of short wave therapy on the nervous system but that similar results might be obtained by an external application of heat.

The portion by Dr. Weissenberg on medical applications is a comprehensive survey of the application of short wave therapy to a great variety of medical and surgical conditions. Both the literature and the author's personal experience are drawn upon in illustrating results.

An introductor chapter describes the biologic action of the waves as due to electrical stimulation of the nervous system with local heat playing but a small rôle.

Both according to theory and the author's experience, lesions most suitable for this form of therapy may be placed in two groups. In the group of superficial inflammations, the local heat and vasodilation produced by the electrical field abort early cases and hastens localization in late. In the organic diseases of the nervous system, particularly diseases of the peripheral nerves, repeated exposure to very weak electrical fields is reported to produce rapid relief of symptoms.

In the field of internal medicine and surgery the cases reported are too few to permit judgment on the merits of this form of therapy. The authors are enthusiastic. It seems probable that short wave therapy will become a valuable adjunct in the symptomatic treatment of systemic disease in

selected cases. That it can lead to a permanent cure throughout the wide range of diseases in which the authors describe its use is extremely doubtful.

The medical section of the book is concise, covering in a page or two each the results of treatment in the various conditions in which it was employed. An attempt is made to state facts without prejudice. From the medical standpoint, this book is of value to those interested in this relatively new field. It provides a base-line upon which future knowledge may be built.

E. P.

THE SPECIFICITY OF SEROLOGICAL REACTIONS. By KARL LANDSTEINER, M.D., The Rockefeller Institute for Medical Research, New York. Pp. 178. Springfield, Ill.: Charles C Thomas, 1936. Price, $4.00.

THOSE interested in the chemical aspects of immunity will welcome this revised edition of Dr. Landsteiner's book, originally published in German, and now re-written for American publication. Although it is based on the extensive investigations of the author and his co-workers, it also represents an exhaustive cross-section of the literature of immunochemistry; and the value of this bibliography is enhanced by its organization into the body of the text.

The book begins with a discussion of the specificity of naturally occurring protein and cell antigens, and a chapter on the specificity of antibodies. There follows a consideration of artificially conjugated antigens, and the reactivity of the corresponding antibodies with simple chemical compounds. The last chapter deals with the recent work on the serologic reactivity of specific cell carbohydrates and lipoids.

The present status of our knowledge of specificity is accurately reflected by the stress placed on the presentation of the actual experimental data rather than their premature interpretation, and by the fact also that in a book of this size, it was found necessary to devote only 14 pages to antibodies.

H. E.

PEDIATRIC NURSING. By JOHN ZAHORSKY, M.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine; Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc., assisted by BERYL E. HAMILTON, R.N., Graduate of St. Luke's Hospital, St. Louis. Pp. 568; 144 illustrations and 7 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, $3.00.

THIS book should be heartily welcomed by pediatric instructors as meeting the needs produced by the rapid changes in this vast field of caring for the sick child and for the proper development of the baby and the well child. The subject material is clearly and simply outlined. Each chapter deals directly with practical points and sound theories as a guide in rendering understandable nursing care to the sick individual. An interesting order of the development from the psychological aspect avoiding the difficult fads of recent years is noted. The book contains common sense indications for guidance of the baby into normal health and natural habits. The nursing points are concise and well emphasized in their descriptive manner.

The illustrations of the technical procedures, of which so many books have too few, are a valuable asset. They serve as a reminder of the demonstrations given to the students and portray a clear picture of the technique.

The chapters on "Home and the Family" and "Child Psychology" bring a refreshing appeal to the reasonable sensible approach of the parents and the nurse in managing the child. A wide scope of information is given to enlighten those who devote their time in caring for babies in an intelligent wholesome humane way.

B. L.

1ère Semaine Médicale Internationale en Suisse, Montreux, 9–14 Septembre, 1935. Organisée par le Journal Suisse de Médecine. Sous le patronage du Haut Conseil Fédéral de la Confédération Suisse. Pp. 477; illustrated. Bale: Benno Schwabe & Cie, 1936. Price, Sw. Fr. 20.

This report of the first Swiss International Medical Week plunges so abruptly *in medias res* that one can find nothing about the nature of the gathering except that it was organized by the Swiss Journal of Medicine, under the patronage of the Federal Council of Switzerland and was attended by some 250 doctors from several countries. The 29 addresses, many by well-known European authorities, are grouped under the general headings of General Therapy, Vitamines and Hormones (included in this section is Sigerist's "The Present Unrest in the Medical World!"), Internal Medicine, Pediatrics and Nutrition, Cancer and Radiation Therapy, and Actual Problems (!). The various presentations, as might be expected, show a considerable variation of excellence. E. K.

The Baby and Growing Child. Feeding and Health Care for Physicians, Mothers and Nurses. By Louis Fischer, M.D., Consulting Physician to the Willard Parker Hospital, New York City, and St. Vincent's Hospital, Montclair, N. J., etc. Pp. 260; many illustrations, some in colors. New York: Funk & Wagnalls Company, 1936. Price, $1.50.

In the opinion of the Reviewer, this is another volume on the care of children which goes too far in what it attempts. It would seem reasonable to suppose that a certain amount of standard and fundamental information should be placed at the disposal of young mothers. In the opinion of the Reviewer, and this opinion is shared by many other pediatricians, this body of fundamental facts can be condensed into a very short volume. It is not good judgment to encourage the diagnosis and treatment of disease or disorders of nutrition by the laity. E. T., Jr.

Protoplasm. By William Seifriz, Ph.D., Professor of Botany, University of Pennsylvania, Philadelphia. Pp. 584; 179 illustrations. New York: McGraw-Hill Book Company, Inc., 1936. Price, $6.00.

The subject of this book is "living matter in its simplest form." Though the description of Dujardin, the discoverer of protoplasm (1935), is still "as accurate as any that can be given," and though this presentation is for students in biology and medicine in form "as nontechnical as is consistent with accuracy and completeness (!)" yet a wide range is covered in a way that demands careful study by colleagues as well as students. Exemplifying the opening quotation from Descartes on the interdependence of science, the 27 chapters proceed from such technical fields as micrurgy and tissue culture to 9 chapters on the biophysics of colloids, osmosis, elasticity and so on; 2 on electrophysiology; 5 on the biochemistry of salts, carbohydrates, fats, proteins and regulatory substances; concluding with one on "the origin of living matter." This predominantly physical approach is in line with the Zeitgeist, as is the avoidance of "severely adverse or destructive criticism and finality in statement, for both are out of place in science, especially today, when change and doubt are the very spirit of scientific thought." Lacking the special knowledge that the author so obviously possesses, the Reviewer refrains from any attempt to criticize the subject matter; he has a strong impression that this is an accurate presentation of an important subject in an able, up-to-date manner. E. K.

NEW BOOKS.

A Manual of Practical Obstetrics. By O'DONEL BROWNE, M.B., B.CH., B.A.O., F.R.C.P.I., L.M. (Rotunda Hospital), M.C.O.G., Assistant Gynaecologist, Sir Patrick Dun's Hospital, Dublin; Assistant to the Professor of Midwifery, Trinity College, Dublin. Pp. 363; 236 illustrations and 10 plates, some in color. Baltimore: William Wood & Co., 1936. Price, $6.50.

The Thyroid. Surgery, Syndromes, Treatment. By E. P. SLOAN, M.D. Edited by Members of the Sloan Clinic: GUY A. SLOAN, M.D.; H. P. SLOAN, M.D.; FRANK DENEEN, M.D.; H. W. WELLMERLING, M.D.; O. H. BALL, M.D., and with a Foreword by WILLIAM SEAMAN BAINBRIDGE, M.D. Pp. 475; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, $10.00.

The Toxaemias of Pregnancy. By DAME LOUISE MCILROY, D.B.E., LL.D., M.D., D.Sc. (GLASG.), D. Sc. (LOND.), D. Sc., HON. (BELFAST), F.C.O.G., M.R.C.P., Consulting Obstetrician and Gynaecological Surgeon, Royal Free Hospital; Surgeon, Marie Curie Hospital, etc. Pp. 355; 19 illustrations. Baltimore: William Wood & Co., 1936. Price, $5.00.

Diätetik. Die Ernährung des Gesunden und des Kranken. By Privatdozent DR. WILHELM HEUPE, Oberarzt an der medizinischen Universitäts-Poliklinik, Frankfurt A. M. Band XX of Medizinische Praxis, Sammlung für ärztliche Forbildung. Pp. 192. Dresden: Theodor Steinkopff, 1936. Price: Paper, Rm. 9.50; bound, Rm. 10.80.

Tissue Immunity. By REUBEN L. KAHN, M.S., D.Sc., University of Michigan, Ann Arbor. Pp. 707; illustrated. Springfield, Ill.; Charles C Thomas, 1936. Price, $7.50.

NEW EDITIONS.

The Operations of Surgery. Vol. 1. The Upper Extremity, The Head and Neck, The Thorax, The Lower Extremity, The Vertebral Column. By R. P. ROWLANDS, M.S. (LOND.), F.R.C.S. (ENG.), Late Surgeon to Guy's Hospital; Late Lecturer on Surgery to the Medical School, and PHILIP TURNER, B.Sc., M.S. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to Guy's Hospital; Formerly Lecturer on Surgery and Teacher of Operative Surgery to the Medical School. Pp. 1043; 435 illustrations (38 in color). Eighth edition. Baltimore: William Wood & Co., 1936. Price, $10.00.

An Index of Treatment. By various writers. Edited by ROBERT HUTCHINSON, M.D., LL.D., F.R.C.P., Consulting Physician, London Hospital, and Hospital for Sick Children, Great Ormond Street. Pp. 1020; 147 illustrations. Eleventh edition, revised. Baltimore: William Wood & Co., 1936. Price, $12.00.

Blutung und Fluor. By PROF. DR. HANS RUNGE, Direktor der Universitäts-Frauenklinik Heidelberg. Band IX of Medizinische Praxis. Sammlung fur ärztliche Fortbildung. Pp. 117; 18 illustrations. Second enlarged edition. Dresden: Theodor Steinkopff, 1936. Price, paper, Rm. 7; bound, Rm. 8.

A Textbook of Pathology. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1277; 697 illustrations. Sixth edition, entirely reset. Philadelphia: W. B. Saunders Company, 1936. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
CHARLES C. NORRIS, M.D.,
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,
AND
FRANK B. BLOCK, M.D.,
SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

MALIGNANT TUMORS OF THE UTERINE BODY.

In the present review, as the title indicates, we shall exclude the more common carcinoma of the cervix and confine ourselves to several malignant neoplasms which involve the fundus of the uterus, the most common of which is adenocarcinoma. In order to obtain anything like a satisfactory result in dealing with uterine cancer, it is necessary to make an early diagnosis. Of all symptoms which should make us suspicious of this disease, the most important is postmenopausal bleeding, which, however, does not always indicate the presence of cancer. This subject has been studied in a series of 315 cases of postmenopausal hemorrhage by Schulze,[1] who found that in 215 cases, or more than two-thirds of the total number, the bleeding was due to a malignant tumor of the genital tract and of these the very great majority were uterine tumors. Carcinoma of the cervix was present in 153 patients, in 14 of which the carcinoma had developed in the cervical stump following supravaginal hysterectomy. The histologic diagnosis of adenocarcinoma of the stump appearing rather soon after supravaginal hysterectomy aroused the suspicion in 3 of these cases that the tumor might have arisen from a fundal adenocarcinoma overlooked at the primary operation. Fifty-one women in the series had fundal adenocarcinoma, 2 had sarcoma and 1 had a chorioepithelioma; 3 women had vaginal carcinoma, 2 had urethral carcinoma and 1 had a vulvar cancer. Among the ovarian tumors associated with postmenopausal hemorrhage were 2 ovarian cancers and 2 granulosa cell tumors. Benign tumors causing bleeding are relatively infrequent in older women. There were only 5 myomata in the series but mucous polypi, both of the fundus and of the cervix are comparatively common and are usually an obvious cause of hemorrhage. Other more or less common causes of postmenopausal bleeding are: that due to trauma to a prolapsed uterus, ill fitting pessaries, senile vaginitis, trichomonas infestation, urethral caruncle and endocervicitis. This study shows that by no means all postmenopausal bleeding is due to fundal cancer, but it also shows that this disease is common enough in patients who present this symptom, that in the absence of any obvious

explanation of the bleeding, cancer must be considered as probable until it is definitely excluded.

A study of case histories of patients with fundal cancer at The Mayo Clinic has been made by Judd, Phillips and Waldron.[2] They found that the patients usually come for consultation because of a troublesome vaginal discharge or because of some irregularity in the menstrual cycle, and that ordinarily pain is not a feature of the complaint until later in the course of the disease. A persistent increase in the menstrual flow, or spotting between the periods after the age of 35 years should be carefully investigated, particularly if it occurs after the menopause. They found that between 60 and 65% of carcinomas of the uterine body are observed after the menopause. Fortunately, carcinoma of the body of the uterus has a tendency to be confined to the endometrium and does not invade the muscular wall of the uterus or extend to the peritoneum for a considerable time. This is partially explained by the fact that the lesions are usually not of the active type as classified according to Broders' index of malignancy, being usually of Grade 1 or 2. Extension to the lymph nodes is uncommon because the uterine muscle limits the growth and forms a barrier to the lymph channels so that there is a satisfactory response to treatment in many cases in spite of the duration and local extent of the disease.

Some interesting biometric studies on endometrial cells have been made by McCormack,[3] who measures the size of the nucleus and nucleolus of cells of the uterine glands in various pathologic conditions, to determine the relation that exists between them, especially in benign as contrasted with malignant conditions. Forty-eight specimens of endometrium were studied; these consisted of 34 specimens of hypertrophied endometrium, 4 of adenomyoma, 6 of polypoid endometrium, and 4 of adenocarcinoma. Twenty cells in each of the 48 specimens were studied. In malignant tissue, sections of the nuclei average 64.9 square microns in area, while in benign tissue, sections of the nuclei average 51.7 square microns. In malignant tissue, sections of the nucleoli average 3.9 square microns in area while in benign tissue they average only 1.4 square microns. In malignant cells the ratio in size of nucleolus to nucleus is 1:16.6 while in benign cells this ratio is 1:36.9. This study shows clearly that the important biometric differences between malignant and benign cells are: (1) the larger nucleus and nucleolus in the malignant cell, and (2) the smaller ratio that exists between the size of the nucleolus and nucleus in the malignant cell.

While it usually assumed that all cancers of the fundus of the uterus are adenocarcinomas, it should be remembered that in exceptional instances the growth may be a *squamous cell carcinoma*. Gellhorn[4] has reported 2 personal observations of this type to be added to the very scanty international literature on the subject. Of course, squamous cell cancer cannot develop directly from the cylindrical epithelium of the endometrium. There must first occur as a connecting link a change from the cylindrical to the pavement epithelium. This metaplasia may be either the result of certain conditions acquired during the lifetime of the individual or it may be the expression of a faulty embryonic development.

Surgical Treatment. In order to determine whether operation or irradiation gives the better results in fundal cancer, Nordmeyer[5] analyzes the results from the gynecologic clinic at Goettingen and compares

them with the world literature on the subject. At his clinic, from 1926 to 1930, there were 78 cases of fundal cancer, all microscopically proven. Of these, 62 were operable and 16 inoperable. The absolute cure rate, (that is, the percentage of cures to the total number seen) was 46.1%. The relative healing of the operable cases was 58%, while there were no cures in the inoperable cases. Of the operable cases 34 were treated by surgery and 28 by irradiation. Of the 34 operated upon, 24 were cured (70.6%), while of the 28 treated by irradiation, 12 were cured (42.9%). The primary mortality of operation was *nil* while irradiation gave a primary mortality of 9.1%. In the world literature which he collected, surgery gave a cure rate of 56.8% against a rate of 50.5% for irradiation.

Reporting from Stoeckel's clinic in Berlin, Volbracht[6] states that in the period from 1926 to 1930 they treated 112 patients, of which 70 were operated upon with a mortality of 7.1% with a recurrence rate of 25.7% and a 5-year curability of 67.1%. Of the 42 who were treated by irradiation alone there was a primary mortality of 2.4% recurrence in 50% and a 5-year cure in 47.6%. As a result of this comparison he believes that operation is the treatment of choice, especially since the rate of operability is high. Of course radium irradiation must be used in the inoperable cases and in those in whom surgery is contraindicated because of associated serious systemic disease.

Beattie[7] calls attention to the fact that several histologic types of adenocarcinoma may be found in any one specimen so that it is impossible, in all cases, to diagnose the histologic nature of the main mass of a carcinoma from curettings alone. For this reason he believes that the prognosis cannot always be based upon the histologic report, as so many investigators, particularly in this country, have stated in recent years. As to treatment, his series has shown to his satisfaction that surgery is the method of choice, since surgery with or without supplementary irradiation gave 58% of 5-year cures as opposed to 18% of 5-year cures in the cases receiving irradiation alone.

In reporting a series of 56 patients which they treated, Newell and Crossen[8] state that in comparing the results of different methods of treatment for any grade of corpus carcinoma, the comparison should be made with cases of the same approximate extent, that is, early cases to early cases and late cases to late cases. Otherwise there may be erroneous conclusions as to the efficacy of the different methods of treatment. This point is illustrated by their series in which death resulted in nearly all patients receiving only irradiation, which would seem to indicate that irradiation has very little curative effect. But when the extent of the disease is considered, we find that practically all cases presenting reasonable hope of cure were subjected to operation, irradiation alone being limited to the hopeless cases. They feel at present that operation plus irradiation is the safest plan of treatment. If the patient is a good operative risk, hysterectomy is performed and is supplemented by irradiation to devitalize any cancer cells which may be beyond the structures removed. This may be given before or after the operation or both, and may be given by Roentgen ray or radium or both. In their series 20 cases were treated by operation alone with 13 cures for over 5 years, 23 were treated by operation plus irradiation with 14 cures for over 5 years, while irradiation alone gave only 2 cures in 13 cases treated.

At The Mayo Clinic, according to Judd, Phillips and Waldron,[2]

total abdominal hysterectomy with removal of both tubes and ovaries is the preferable treatment because of the tendency of carcinoma in this location to be of low grade and to remain localized.

Removal of the tubes and ovaries is essential, for it precludes the possibility of development of secondary growths from malignant cells that may have migrated to these tissues. The immediate mortality rate is lower following this operation than it is after hysterectomy of the Wertheim type. Such satisfactory results have been obtained by them that they have been encouraged to extend the operation to some cases in which widespread involvement precluded anything more than temporary relief. In many of these cases it has controlled the process for a much longer period than could reasonably have been anticipated. Late in the course of the disease the bladder, rectum and vagina may be involved in a solid carcinomatous mass. In these cases and in those in which the risk of surgical procedure is definitely out of proportion to the benefit to be obtained, the use of radium may have some palliative effect.

Irradiation Therapy. Based upon the results obtained in his large experience at the Memorial Hospital in New York, Healy[9, 10, 11] has become a strong advocate of irradiation therapy in fundal cancer. He states that for a long time it has been generally assumed that, since carcinoma of the corpus is a glandular variety of cancer, it is radiation resistant, and irradiation therapy could not be used to advantage to control tumor growth. However, irradiation has been used in patients who declined operation or were poor risks for major surgery and it has been noted that such patients were often benefited and at times apparently cured. Moreover, it was recognized that a great many patients in whom hysterectomy had been done did not remain well but developd local recurrences or distant metastases 2 or 3 years after operation and ultimately died of cancer. He divides corpus cancers into four histologic groups:

1. Papillary adenoma malignum. The growth is entirely papillary and may not be superficial but as a rule does not tend to invade the myometrium. It resembles adenomatoid endometritis and the cells show very little change from the normal.

2. Adenoma malignum. The microscopic picture is characterized by large or giant glands, often greatly elongated, lined by several layers of cuboidal and cylindrical cells. The stroma is greatly reduced and the enlarged glands adjoin each other, often in groups of 3 or 4 surrounded by strands of stroma. The nuclei of the gland cells are large and hyperchromatic and stain deeply. Any tendency on the part of the cells to break through into the stroma and to form solid masses takes the tumor out of this group and places it in the next one.

3. Adenocarcinoma. Histologically the cases in this group are characterized by greater malignancy. The cells are more atypical and there is more evidence of anaplasia than in the preceding groups and the tumor while still retaining its glandular arrangement, nevertheless infiltrates the stroma and forms solid masses of tumor cells. It is this evidence of infiltration which distinguishes this group from the preceding one.

4. Cellular (anaplastic) adenocarcinoma. Cases in this group are characterized histologically by diffuse growth of small round cells and polyhedral cells often entirely lacking in glandular arrangement. The

cells may be closely packed together, stroma scanty, mitotic figures numerous and marked evidence of anaplasia is seen.

Healy observes that 100% of all Group 1 patients and 87.5% of Group 2 patients are alive, regardless of the plan of treatment followed. This would seem to indicate that the disease in these histologic types remains localized in the uterus for a long time and if the risk of hysterectomy is not too great, a cure may be obtained by this procedure. On the other hand, when operation is contraindicated, irradiation may be carried out to advantage. He believes it is highly significant that the patients in whom irradiation was used in full dosage, either alone or some weeks before hysterectomy have remained free from recurrent or metastatic disease and have lived longer than those patients treated by hysterectomy before irradiation or by hysterectomy alone. In view of the marked difference in end results in the two major histologic types represented by the adenoma malignum type and the adenocarcinoma type and therefore, the prognostic value of knowing as soon as possible the histologic type in which the particular case falls, it would seem highly desirable to obtain tissue from within the uterus for microscopic study before even curettage is done. If this is not possible, a quick report from either frozen section at the time of curettage or in 4 or 5 hours would be helpful in planning treatment. In adenocarcinoma, even if the patient is in condition for hysterectomy, he believes that it is best to institute a full dosage of intrauterine irradiation supplemented by deep Roentgen ray therapy previous to hysterectomy. Also in order to permit the full effect of irradiation to be obtained the operation should be delayed from 4 to 6 weeks following irradiation. Postoperative irradiation with radium applied in capsules throughout the length of the vaginal tube and a Roentgen ray cycle should be utilized as an additional precautionary measure 8 to 12 weeks after hysterectomy in cases of adenocarcinoma. In his experience 39% of the patients with adenocarcinoma die within 3 years, whereas in the adenoma malignum varieties only 7% die within the first 4 years. Two interesting observations have been made on this combined method of treatment; first, the hysterectomy has not been made more difficult because of the preoperative irradiation and, second, very little viable cancer and in more than half the cases no cancer at all could be found in the uterus on microscopic examination after its removal. In his series of 134 cases there has been no operative mortality. In the cases treated by irradiation alone, it is desirable to check the result by an exploratory curettage about 12 to 16 weeks later and if cancer is found further irradiation therapy is indicated, or if possible the uterus should be removed.

At the Woman's Hospital in New York, Ward[12] found that carcinoma of the fundus occurs in about 10% of the cases of uterine cancer, and since 1919 there have been 134 such cases in that hospital. Of the 92 patients who have been treated, 61 received irradiation alone, 25 were treated by radium and hysterectomy, and 6 received operation alone. As this type of disease is more frequent in the later decades of life, many patients are poor operative risks on account of old age, obesity, cardiovascular disease, deficient renal function or diabetes. These complications were present in more than 50% of his cases, so that radiotherapy alone had to be relied upon.

Voltz[13] states that from 1913 to 1928 in the irradiation clinic of Doederlein in Munich, there were 138 cases of fundal cancer treated by

irradiation, of whom 56 (40.6%) were alive and free from disease 5 years later.

Sampson[14] is of the opinion that radium is of value in those cases in which it can be brought into intimate contact with the growth, but as a result of his laboratory studies he has found that in many instances it is a matter of chance as to whether the radium gets into such intimate contact. He has made skiagrams of uteri removed at operation, with and without carcinoma of the body, in which capsules have been placed just as would be done in the radium treatment. He found that the radium may not get into intimate contact with the cancer due to faulty technique in placing the capsules, large uterine cavities, cavities of the Y type with carcinoma in one or both cornua, intramural myomas or polyps which deflect the capsules or shield part of the growth from the radium and bulky carcinomas which distend the uterine cavity. Unfortunately the presence of such conditions can be determined with certainty only after the organ has been removed and even then there may be metastases to other organs which cannot be detected. However, in spite of the uncertainties of the intrauterine application of radium, he believes that it is of the greatest value in many instances. We are much better able to judge the condition of the patient as a surgical risk than we can foretell if all of the growth can be reached by radium. Because of the inability to make an accurate pretreatment diagnosis of the exact situation and extent of the growth and the fact that all of the carcinoma may sometimes be removed where radium would fail, he believes that the removal of the entire uterus, tubes and ovaries is indicated in patients who are good surgical risks. Radium is indicated in hazardous surgical risks, especially when the uterus is small and the adnexa are not enlarged and also in evident irremovable carcinomas.

Chorioepithelioma. Although in discussions concerning malignancy of the uterus the type known as chorioepithelioma is always considered, in reality it is quite a rare disease and few clinics have an opportunity of observing more than a very occasional case. In discussing this subject, Black[15] presents the important points to be remembered in connection with its diagnosis and treatment. He stated that a uterine hemorrhage or a blood tinged discharge following pregnancy (especially a hydatidiform mole) with a positive Aschheim-Zondek test, should arouse suspicion of a chorioepithelioma. It should be remembered that while almost half of the cases follow moles, only about 1% of moles are followed by chorioepitheliomas: therefore, a hysterectomy or large doses of radium are not justifiable in young women with moles. In the cases which have been definitely diagnosed chorioepithelioma from the histologic examination of the curettings, especially in the presence of a typical clinical history, a panhysterectomy should be performed and irradiation treatment instituted. As embryonic cells are very sensitive to radium rays, radium is a good prophylactic and curative agent in selected cases. Repeated Aschheim-Zondek tests following moles and especially hysterectomy for chorioepithelioma are of paramount prognostic importance, since the pregnancy reaction in mice is twelve times stronger in a mole and chorioepithelioma than in a 2-months' gestation, so that the persistence of the reaction after labor or abortion should be regarded with suspicion. On the other hand, if such patients present a

negative reaction to the test, one may feel reasonably assured of no further trouble.

Mathieu and Palmer[16] feel that in the light of our present knowledge, chorioepithelioma can be definitely diagnosed shortly after its inception. They believe that every patient who passes a mole should have her urine examined for anterior pituitary-like hormone by the Friedman test monthly for a year at least. In this way a developing chorioepithelioma might be diagnosed and removed before symptoms appear or before metastases develop. They report 2 cases in which the diagnosis was made early in this way, the patients operated upon and cured. The first case was diagnosed 2 months and 4 days, the second 3 months and 4 days after the passage of a mole. They believe that their first case is unique. Following the curettage for the removal of the hydatid material the patient was absolutely free from symptoms. There was no more bleeding, her blood count increased, the uterus and pelvic contents were normal to palpation, she was in good health, free from complaints and had gained weight. There was no cough nor any sign of lung involvement. The sedimentation rate remained slightly increased and the Friedman test was persistently positive. In all the other cases reported there was bleeding, signs of metastases, enlargement of the uterus or some other signs of chorioepithelioma. The question of removal of the ovaries in conjunction with hysterectomy for this disease will bear discussion. In other forms of malignancy there will be less danger of recurrence if a complete operation is done. However, these authors believe that in cases of chorioepithelioma diagnosed early, one need not remove the ovaries. In their first case only a supravaginal hysterectomy was done and there was no evidence of recurrence. In the second case a complete hysterectomy was done because of severe lacerations of the cervix, and the right ovary was removed only because it was adherent.

Leventhal and Saphir[17] state that prior to the utilization of the Aschheim-Zondek test most cases of chorioepithelioma were not diagnosed until a uterine mass was palpable, until a curettage brought forth characteristic tissue or until metastases in the lungs or vagina appeared. Often a mass was not palpated until metastases had appeared. Curettage as a diagnostic method not only is uncertain because of the possible location of the tumor at a distance from the endometrium but is dangerous, because the site of a friable growth may be perforated. The use of the Aschheim-Zondek test following a mole obviates the necessity of a curettage and its attendant dangers and is a diagnostic method by which very early chorioepithelioma may be revealed, even before a tumor is palpable or hemorrhage occurs. In the quantitative hormone test an additional method becomes available. In normal pregnancy the concentration of anterior pituitary-like substance in the urine begins to diminish after the sixth or eighth week. In a hydatidiform mole the concentration increases progressively and rapidly. In the absence of clinical manifestations, an amount of gonadotropic substance in the urine in excess of 20,000 mouse units per liter indicates an early chorioepithelioma. They diagnosed an early case solely on the basis of the laboratory finding of 333,000 mouse units in a patient who had expelled a mole $4\frac{1}{2}$ months previously. Recurrence of the disease or metastases may be discovered by the Aschheim-Zondek reaction, and this should determine the use of radiation therapy.

Mazer and Edeiken[18] caution that abnormal bleeding following a normal pregnancy or a mole should not be treated by radium because it masks the symptoms of chorioepithelioma and they also believe that it is impossible to make an early diagnosis of this tumor by means of uterine curettage. The source of the hormone responsible for the Aschheim-Zondek reaction is living chorionic epithelium which should not persist longer than 2 weeks after the termination of a normal pregnancy or 8 weeks after the expulsion of a mole. The quantity of the hormone excreted is proportional to the amount of abnormal chorionic epithelium present, hence a gradual increase in its excretion, with accompanying uterine bleeding following a pregnancy is indicative of chorioepithelioma.

An interesting case reported by Feiner[19] is that of a 28-year-old woman in whom a vaginal tumor developed, possessing the histologic structure of a chorioepithelioma, 2½ years after the last demonstrable pregnancy. In view of the number of similar cases which have been reported, he believes that whereas in the vast majority of cases all fetal elements are destroyed by the maternal tissue within a comparatively short time after the termination of pregnancy, in exceptional instances fetal epithelia may remain dormant in the maternal host, either at the placental site or elsewhere for months or years and then be stimulated to malignant proliferation by some unknown agency. The fact that many of these cases have developed long after the menopause would effectually disprove the theory that in all such cases an intervening pregnancy has escaped detection.

Sarcoma. A group of 43 cases of sarcoma of the uterus has been analyzed by Kimbrough[20] in connection with a review of the literature dealing with the results of treatment. The incidence of sarcomatous degeneration in his series of myomas, as well as in the cases collected from the literature was 0.76%. The total 5-year salvage was 34.3% but taking only the 20 operable cases the 5-year salvage was 50%. The prognosis in sarcomatous degeneration of a myoma is three times more favorable than in primary sarcoma and likewise the salvage in younger women is more than three times as great as in women who have passed the menopause. Considering the histologic types, he found that the small round cell and polymorphous tumors are more highly malignant than the spindle cell sarcoma. As would be expected, the recurrences after operat on were more than twice as frequent in those tumors which presented a large number of mitotic figures as in the tumors with relatively low counts and conversely, the 5-year salvage was almost four times as great in the low count groups as in the tumors showing more numerous mitoses. Therefore, although mitosis merely indicates rapid growth, from a clinical standpoint the number of mitotic figures is a reliable gauge of the degree of malignancy and hence is of prognostic value.

FRANK B. BLOCK, M.D.

REFERENCES.

1. Schulze, M.: Postmenopausal Hemorrhage, Calif. and West. Med., **39**, 158, 1933.

2. Judd, E. S., Phillips, J. R., and Waldron, G. W.: Curability of Carcinoma of the Body of the Uterus, Proc. Staff Meet. Mayo Clinic, **8**, 447, 1933.

3. McCormack, C. J.: Biometric Studies of Endometrial Cells, Ibid. **10**, 24, 1935.

4. Gellhorn, G.: Primary Squamous Cell Carcinoma in The Body of the Uterus, Am. J. Obst. and Gynec., **31**, 372, 1936.
5. Nordmeyer, K.: Die Therapie des Korpuskarzinoms: Operation oder Bestrahlung? Zentralbl. f. Gynäk., **59**, 1415, 1935.
6. Volbracht, R.: Bericht ueber Behandlungserfolge beim Korpuskarzinom, Ibid. **60**, 796, 1936.
7. Beattie, J.: Carcinoma of the Body of the Uterus; Study of 50 Cases, J. Obst. and Gynec., Brit. Emp., **40**, 768, 1933.
8. Newell, Q. U., and Crossen, H. S.: Five-year Results in Fifty-Six Cases of Carcinoma of Corpus Uteri, Am. J. Obst. and Gynec., **29**, 326, 1935.
9. Healy, W. P.: Evaluation of Radiation Therapy in Malignant Disease of Female Generative Tract, Ibid., **26**, 789, 1933.
10. Healy, W. P.: Radiation Therapy in Carcinoma of Corpus Uteri, Ibid., **27**, 1, 1934.
11. Healy, W. P.: Irradiation Therapy in Cancer of Corpus Uteri: Indications and Technique, Am. J. Surg., **27**, 401, 1935.
12. Ward, G. G.: Evaluation of Radiotherapy for Carcinoma of Uterus after 15 Years' Experience at Woman's Hospital, South. Med. J., **29**, 282, 1936.
13. Voltz, F.: Weitere Ergebnisse der Strahlenbehandlung des Uteruskarzinoms, Zentralbl. f. Gynäk., **58**, 2466, 1934.
14. Sampson, J. A.: Limitations and Dangers of Intrauterine Application of Radium in Treatment of Carcinoma of the Body of the Uterus, Am. J. Obst. and Gynec., **28**, 783, 1934.
15. Black, W. T.: Chorioepithelioma of the Uterus, Am. J. Surg., **20**, 638, 1933.
16. Mathieu, A., and Palmer, A.: Early Diagnosis of Chorioepithelioma, Surg., Gynec. and Obst., **61**, 336, 1935.
17. Leventhal, M. L., and Saphir, W.: Chorioepithelioma: Early Diagnosis by Quantitative Determination of Anterior Pituitary-like Principle from the Urine of Pregnancy, J. Am. Med. Assn., **103**, 668, 1934.
18. Mazer, C., and Edeiken, L.: Value of Aschheim-Zondek Reaction in Diagnosis and Prognosis of Chorionephitheloma, Am. J. Obst. and Gynec., **26**, 195, 1933.
19. Feiner, D.: Chorionepithelioma with Long Latent Period, Ibid., **29**, 840, 1935.
20. Kimbrough, R. A., Jr.: Sarcoma of the Uterus: Factors Influencing Results of Treatment, Ibid., **28**, 723, 1934.

Notice to Contributors. Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the articles and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers). Titles can be included for less than 25 references.

Return postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

Two hundred and fifty reprints, with covers, are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.